(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 221 444 B1

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention of the grant of the patent:
31.08.2005 Bulletin 2005/35

(21) Application number: **00940909.5**

(22) Date of filing: **30.06.2000**

(51) Int Cl.[7]: **C07D 473/34**, C07D 473/18, C07D 471/08, C07D 473/40, C07D 239/48, C07D 213/73, C07D 213/75, C07D 235/18, C07D 471/04, C07D 487/04, C07D 401/12 // (C07D471/04, 235:00, 221:00), (C07D401/12, 239:00, 213:00)

(86) International application number:
PCT/JP2000/004358

(87) International publication number:
WO 2001/002400 (11.01.2001 Gazette 2001/02)

(54) **FUSED IMIDAZOLE COMPOUNDS AND REMEDIES FOR DIABETES MELLITUS**

KONDENSIERTE IMIDAZOLDERIVATE UND ARZNEIMITTEL GEGEN DIABETES MELLITUS

DERIVES D'IMIDAZOLE CONDENSES ET MEDICAMENTS CONTRE LE DIABETE SUCRE

(84) Designated Contracting States:
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE

(30) Priority: **02.07.1999 JP 18848499**
16.05.2000 JP 2000143495
19.06.2000 JP 2000182786

(43) Date of publication of application:
10.07.2002 Bulletin 2002/28

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Description

Field of the Invention

[0001] The present invention relates to a novel purine compound having a hypoglycemic action and a glucose tolerance improving action on the basis of an inhibitory action on glucose production and a promoting action on glucose utilization at the periphery and to a preventive or therapeutic agent for diabetes mellitus and diabetic complications comprising the purine compound. More specifically, it relates to a novel purine compound which is an adenosine A2 receptor antagonist and to a preventive or therapeutic agent for diabetes mellitus and diabetic complications on the basis of an adenosine A2 receptor antagonist action.

Prior Art

[0002] With regard to therapeutic agents for diabetes mellitus, various biguanide compounds and suflonylurea compounds have been used. However, the biguanide compounds induce lactic acidosis and, therefore, their use is limited while the sulfonylurea compounds often result in severe hypoglycemia due to their strong hypoglycemic action and, therefore, their use is to be careful.

[0003] Diabetic complications are recognized in the eyes, kidney, nervous system, cardiovascular system, skin etc., and frequently occurring complications specific to diabetes mellitus include retinopathy, nephrosis and neuropathy. It is considered that these complications are reduced generally by achieving blood sugar controlled at the normal level or thereabout ("Saishin Igaku Daijiten" (Newest Medical Large Dictionary) published in 1988 by Ishiyaku Shuppan). A major factor for diabetic retinopathy (particularly proliferating retinopathy) is angiogenesis, and activation of an adenosine A2 receptor promotes angiogenesis in the retina due to low oxygen (Takagi, H. et al., Invest. Ophthalmol. Vis. Sci., 37, 1311-1321 and 2165-2176 (1996)).

[0004] Adenosine is a nucleoside widely existing in living body and has a physiological action on the cardiovascular system, central nervous system, respiratory system, kidney, immune system, etc. The action of adenosine is achieved via at least four receptors - A1, A2a, A2b and A3 - in which G protein participates (Fredholm, B. B. et al., Pharmacol. Rev., 46, 143-156, 1994). In 1979, adenosine receptor was at first classified into A1 and A2 on the basis of their pharmacological action and participation in adenylate cyclase (Van Calker, D. et al., J. Neurochem., 33, 999-1003, 1979). Then A2 receptor has classified into the subtypes of A2a and A2b on the basis of high and low affinity for adenosine and for adenosine A2 agonists, i.e. NECA and CGS-21680 (Burns, R. F. et al., Mol. Pharmacol., 29, 331-346, 1986; Wan, W. et al., J. Neurochem., 55, 1763-1771, 1990). Although gradually, physiological and pathological significance of those receptors has been clarified in the central nervous system, circulatory system, etc.

[0005] With regard to glucose metabolism, the following reports have been available. In an experiment using skeletal muscles, adenosine lowers the insulin sensitivity due to an agonistic action on the A1 receptor suppressing the glucose uptake while an A1 receptor antagonist increases the insulin sensitivity (Challis, R. A., Biochem., J., 221, 915-917, 1984; Challis, R. A., Eur. J. Pharmacol., 226, 121-128, 1992). In adipocytes, adenosine enhances the sensitivity of insulin via an A1 receptor, whereby glucose uptake is promoted (Vannucci, S. J., 288, 325-330, 1992). Further, WO 95/18128 and WO 98/03507 disclose a therapeutic agent for diabetes mellitus comprising an A1 receptor antagonist. Thus, there have been many reports on an A1 receptor. With regard to an adenosine A2 receptor, there is a simple description in WO 97/01551 suggesting a therapeutic agent for diabetes mellitus comprising the A2a receptor antagonist although any ground is not mentioned at all. In TIPS., 14, 360-366, 1993, participation of the adenosine A2 receptor in the promotion of gluconeogenesis in hepatic cells is suggested but there is no specific description at all. On the contrary, WO 98/01459 describes a therapeutic agent for diabetes mellitus comprising the A2 receptor agonist but there is no description of the adenosine A2 receptor antagonist at all. As such, the positioning of the adenosine A2 receptor antagonist as a therapeutic agent for diabetes mellitus has been in a chaotic state.

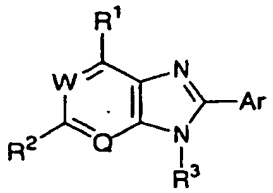
[0006] The object of the present invention is to provide a preventive or therapeutic agent for diabetes mellitus and diabetic complications on the basis of a new action mechanism which is different from that of conventional biguanide compounds and sulfonylurea compounds having several limitations in actual use.

[0007] The present invention relates to a novel purine compound. EP 1054012 A1 and US 4,728,644 disclose different purine compounds. JP-A-10-182636 (wherein JP-A refers to an unexamined Japanese patent application) discloses benzoimidazole compounds having a pyridazinone substituent. WO 98/39344 discloses purine inhibitors of fructose-1,6-bisphosphatase having a phosphate ester group. An article by R. J. Chorvat et. al. (J. Med. Chem., March 1999, Vol. 42, No.5, pp. 833-848) discloses imidazopyrimidines' having an aryl substituent. Another article by R. C. Young et. al.. (J. Med. Chem., 1990, vol. 33, No. 8, pp. 2073-2080) describes various substituted purine derivatives.

Disclosure of Invention

[0008] As a result of extensive study, the present inventors found that an adenosine receptor antagonist serves as a new type of a preventive or therapeutic agent for diabetes mellitus. That is, hyperglycemia in spontaneous diabetic mice was improved by the adenosine receptor antagonist. This action was estimated to attributable to the inhibitory action of the antagonist on both glycogenolysis reaction and gluconeogenesis in the liver promoted by endogenous adenosine. On the basis of this finding, they searched for compounds having an excellent hypoglycemic action and glucose tolerance improving action as a preventive or therapeutic agent for diabetes mellitus, and as a result, they found novel condensed imidazole compounds represented by the following formula (I). As a result of further extensive study for their action mechanism, they found that among adenosine receptor antagonism, an adenosine A2 receptor antagonism is an essential factor for the hypoglycemic action and glucose tolerance improving action, and they arrived at use of the adenosine A2 receptor antagonist as a new type of a preventive or therapeutic agent for diabetes mellitus and diabetic complications, and the present invention was thereby completed.

[0009] The novel condensed imidazole compound of the present invention is a condensed imidazole compound represented by the following formula (I):



(I)

(wherein R^1 represents hydrogen, formula $-NR^4R^5$ (wherein R^4 and R^5 are the same as or different from each other and each represents hydrogen, a C1-C8 alkyl group, or a C3-C8 cycloalkyl group, R^2 represents 1) hydrogen, 2) a halogen atom, 3) a C2-C8 alkynyl group, which may be substituted with a hydroxyl group or C3-C6 cycloalkyl group, 4) a C1-C8 alkyl group or 5) a C1-C8 alkoxy group; R^3 represents a 1,2-dihydro-2-oxopyridyl group which may be substituted with a) a halogen atom or a C1-C6 alkyl group, and whose nitrogen atom may further be substituted with b-1) a C1-C6 alkyl group which may be substituted with a halogen atom, hydroxyl, phenyl C2-C8 alkenyl or an optionally protected carboxyl group, b-2) an optionally substituted C3-C6 cycloalkyl-C1-C4 alkyl group or b-3) an optionally substituted C3-C6 cycloalkyl group, ; Ar represents 1) an optionally substituted phenyl group, 2) an optionally substituted pyridyl group, 3) an optionally substituted furyl group or 4) an optionally substituted thienyl group ; and Q and w are both N or one of Q and W is N and the other is CH,

the above-mentioned condensed imidazole compound, a pharmacologically acceptable salt thereof or hydrates thereof, wherein R^2 is hydrogen atom;

the above-mentioned condensed imidazole compound, a pharmacologically acceptable salt thereof or hydrates thereof, wherein Ar is an optionally substituted phenyl;

the above-mentioned condensed imidazole compound, a pharmacologically acceptable salt thereof or hydrates thereof, wherein Ar is a phenyl substituted with a halogen atom;

the above-mentioned condensed imidazole compound, a pharmacologically acceptable salt thereof or hydrates thereof, wherein R^1 is represented by the formula $-NR^4R^5$ (wherein R^4 and R^5 are the same as or different from each other and each represents hydrogen or, a C1-C8 alkyl group or a C3-C8 cycloalkyl group

the above-mentioned condensed imidazole compound, a pharmacologically acceptable salt thereof or hydrates thereof wherein R^1 is amino;

the above-mentioned condensed imidazole compound, a pharmacologically acceptable salt thereof or hydrates thereof wherein R^1 is amino and R^2 is hydrogen; and R^3 is a 1,2-dihydro-2-oxopyridyl group which may be substituted with a) a halogen atom or a C1-C6 alkyl group, and whose nitrogen atom may further be substituted with b-1) a C1-C6 alkyl group which may be substituted with a halogen atom, hydroxyl, phenyl, C2-C8 alkenyl or an optionally protected carboxyl group; b-2) an optionally substituted C3-C6 cycloalkyl-C1-C4 alkyl group; or b-3) an optionally substituted C3-C6 cycloalkyl group;

the above-mentioned condensed imidazole compound, a pharmacologically acceptable salt thereof or hydrates thereof, wherein R^1 is amino, R^2 is hydrogen, and R^3 is a 1,2-dihydro-2-oxopyridyl group whose nitrogen may be substituted with a C1 to C6 alkyl group which may be substituted with a halogen atom;

the above-mentioned condensed imidazole compound, which is 5-[6-amino-8-(3-fluorophenyl)-9 H-9-purinyl]-1-methyl-1, 2-dihydro-2-pyridinone, and

a pharmacologically acceptable salt thereof or hydrates thereof.

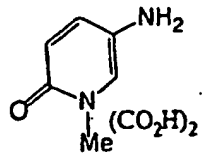
[0010] The present invention provides the condensed imidazole compound of the above formula (I), a pharmacologically acceptable salt thereof or hydrates thereof, which is a purine compound wherein each of Q and W is a nitrogen atom. Further, the present invention provides the condensed imidazole compound of the above formula (I), a pharmacologically acceptable salt thereof or hydrates thereof, which is an imidazopyridine compound wherein one of Q and W is N, and the other is -CH.

[0011] The present invention provides an agent for preventing or treating diabetes mellitus, which comprises the above condensed imidazole compound, a pharmacologically acceptable salt thereof or hydrates thereof as the active ingredient; an agent for preventing or treating diabetic complications, which comprises the above condensed imidazole compound, a pharmacologically acceptable salt thereof or hydrates thereof as the active ingredient; an agent for preventing or treating diseases against which the above condensed imidazole compound, a pharmacologically acceptable salt thereof or hydrates thereof is effective; an agent for preventing or treating diabetic retinopathy, which comprises the above condensed imidazole compound, a pharmacologically acceptable salt thereof or hydrates thereof as the active ingredient; an adenosine A2 receptor antagonist comprising the above condensed imidazole compound, a pharmacologically acceptable salt thereof or hydrates thereof; and a pharmaceutical composition comprising the above condensed imidazole compound, a pharmacologically acceptable salt thereof or hydrates thereof and a pharmacologically acceptable carrier.

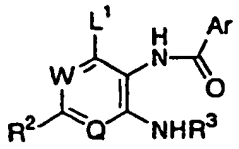
[0012] The present invention provides a method of preventing or treating diabetes mellitus, diabetic complications, diabetic retinopathy or diseases against which the above-mentioned condensed imidazole compound, a pharmacologically acceptable salt thereof or hydrates thereof is effective, or diseases against which an adenosine A2 receptor antagonism is effective, by administering a pharmacologically effective amount of the above-mentioned condensed imidazole compound, a pharmacologically acceptable salt thereof or hydrates thereof.

[0013] Further, the present invention provides use of the above-mentioned condensed imidazole compound, a pharmacologically acceptable salt thereof or hydrates thereof which is used for producing a preventive or therapeutic agent for diabetes mellitus, diabetic complications, diabetic retinopathy or diseases against which the above-mentioned condensed imidazole compound, a pharmacologically acceptable salt thereof or hydrates thereof is effective, or an adenosine A2 receptor antagonist.

[0014] A useful intermediate for synthesis of the compound of the present invention is 5-amino-1-methyl-2(1H)-pyridone oxalate represented by the following formula:

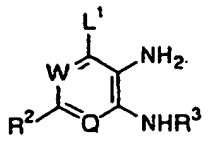


[0015] The present invention relates to a process for producing the compound of the present invention and a synthetic intermediate of the compound of the present invention, that is, a process for producing an acylaminopyridine compound (A3) represented by the following formula:



(A3)

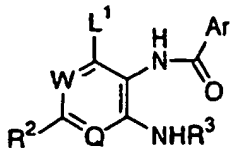
(wherein L^1, R^2, R^3, Ar, Q and W have the same meanings as defined below, respectively), a salt thereof or hydrates thereof, which comprises allowing an aminopyridine compound (A2) represented by the following formula:



(A2)

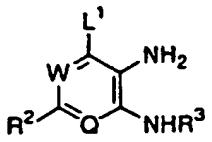
(wherein L^1 represents a halogen atom; R^2 represents 1) hydrogen, 2) a halogen atom, 3) a C2-C8 alkynyl group which may be substituted with hydroxyl group or C3-C6 cycloalkyl group 4) a C1-C8 alkyl group or 5) a C1 - C8 alkoxy group R^3 represents a 1,2-dihydro-2-oxopyridyl group which may be substituted with a) a halogen atom or a C1-C6 alkyl group, and whose nitrogen atom may further be substituted with b-1) a C1-C6 alkyl group which substituted with a halogen atom, hydroxyl, phenyl C2-C8 alkenyl or an optionally protected carboxyl group, b-2) an optionally substituted C3-C6 cycloalkyl-C1-C4 alkyl group or b-3) an optionally substituted C3-C6 cycloalkyl group, and Q and W are both N or one of Q and W is N and the other is CH), to react with an acyl compound represented by the formula ArCOX (wherein X represents a halogen atom; and Ar represents 1) an optionally substituted phenyl group, 2) an optionally substituted pyridyl group, 3) an optionally substituted furyl group or 4) an optionally substituted thienyl group

a process for producing an acylaminopyridine compound (A3) represented by the following formula:



(A3)

(wherein L^1, R^2, R^3, Ar, Q and W have the same meanings as defined above, respectively), a salt thereof or hydrates thereof, which comprises allowing an aminopyridine compound (A2) represented by the following formula:

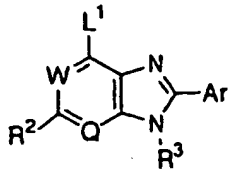


(A2)

(wherein L^1, R^2, R^3, Q and W have the same meanings as defined above, respectively) to react in the presence of pyridine with an acyl compound represented by the formula ArCOX (wherein X and Ar have the same meanings as defined above, respectively) ;

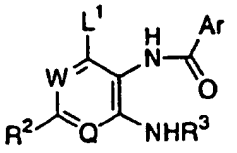
the above-mentioned process for producing an acylaminopyridine compound (A3), a salt thereof or hydrates thereof, wherein R^3 is an N-C1-C8 alkyl-2-oxopyrimidinyl group;

a process for producing an imidazopyridine compound (A4), a salt thereof or hydrates thereof represented by the following formula:



(A4)

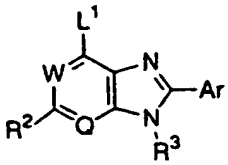
(wherein L^1, R^2, R^3, Ar, Q and W have the same meanings as defined above, respectively), which comprises subjecting an acylaminopyridine compound (A3) represented by the following formula:



(A3)

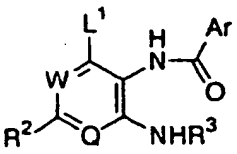
(wherein L^1, R^2, R^3, Ar, Q and W have the same meanings as defined above, respectively) to ring-closure reaction in the presence of $POCl_3$;

a process for producing an imidazopyridine compound (A4), a salt thereof or hydrates thereof represented by the following formula:



(A4)

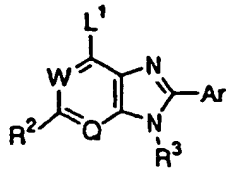
(wherein L^1, R^2, R^3, Ar, Q and W have the same meanings as defined above, respectively), which comprises subjecting an acylaminopyridine compound (A3) represented by the following formula:



(A3)

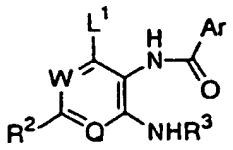
(wherein L^1, R^2, R^3, Ar, Q and W have the same meanings as defined above, respectively) to ring-closure reaction in the presence of hydrochloric acid or using hydrochloride of an acylaminopyridine compound (A3);

a process for producing an imidazopyridine compound (A4), a salt thereof or hydrates thereof represented by the following formula:



(A4)

(wherein L^1, R^2, R^3, Ar, Q and W have the same meanings as defined above, respectively), which comprises subjecting an acylaminopyridine compound (A3) represented by the following formula:

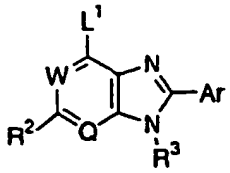


(A3)

(wherein L^1, R^2, R^3, Ar, Q and W have the same meanings as defined above, respectively) to ring-closure reaction in NMP (1-methyl-2-pyrrolidone) under heating;

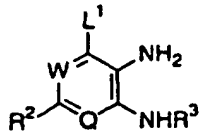
the above-mentioned process for producing an imidazopyridine compound (A4), a salt thereof or hydrates thereof, wherein R^3 is an N-C1-C8 alkyl-2-oxopyridinyl group;

a process for producing an imidazopyridine compound (A4), a salt thereof or hydrates thereof represented by the following formula:



(A4)

(wherein L^1, R^2, R^3, Ar, Q and W have the same meanings as defined above, respectively), which comprises allowing an aminopyridine compound (A2) represented by the following formula:

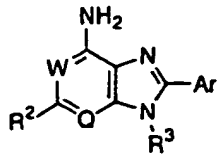


(A2)

(wherein L^1, R^2, R^3, Q and W have the same meanings as defined above, respectively) to react with an acyl compound represented by the formula ArCOX (wherein X and Ar have the same meanings as defined above, respectively); and then subjecting the product to ring-closure reaction;

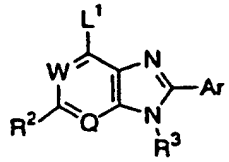
the above-mentioned process for producing an imidazopyridine compound (A4), a salt thereof or hydrates thereof, wherein the aminopyridine compound (A2) is converted in one-pot reaction into the imidazopyridine compound (A4);

a process for producing an aminoimidazopyridine compound (A5), a salt thereof or hydrates thereof represented by the formula:



(A5)

(wherein L^1, R^2, R^3, Ar, Q and W have the same meanings as defined above, respectively), which comprises aminating an imidazopyridine compound (A4) represented by the following formula:

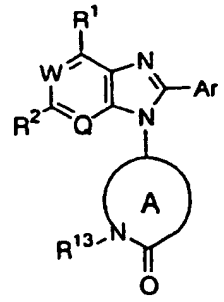


(A4)

(wherein L^1, R^2, R^3, Ar, Q and W have the same meanings as defined above, respectively);

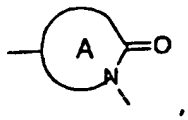
the above-mentioned process for producing an aminoimidazopyridine compound (A5), a salt thereof or hydrates thereof, wherein R^3 is an N-C1-C8 alkyl-2-oxopyridinyl group; and

a process for producing an imidazopyridine compound (C3), a salt thereof or hydrates thereof represented by the formula:

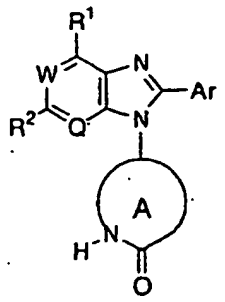


(C3)

(wherein R^{13} means a C1-C6 alkyl group which may be substituted with a halogen atom, hydroxyl or an optionally protected carboxyl group, an optionally substituted C3-C6 cycloalkyl-C1-C4 alkyl group, or an optionally substituted C3-C6 cycloalkyl group; and R^1, the formula:

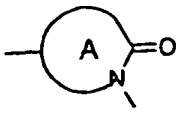


R^2, Ar, Q and W have the same meanings as defined above, respectively), which comprises alkylating an imidazopyridine compound (C2) represented by the following formula:



(C2)

(wherein R^1 represents hydrogen atom, or formula $-NR^4R^5$ (wherein R^4 and R^5 are the same as or different from each other and each represents hydrogen atom or a C1-C8 alkyl group ; the formula:



represents dihydrooxopyridinyl and R^2, Ar, Q and W have the same meanings as defined above, respectively.

[0016] In the definition of R^3 and Ar in the formula (I), the term "optionally substituted", for example an optionally substituted phenyl group, an optionally substituted pyridyl group, an optionally substituted C1-C8 alkyl group etc., means that each group may be substituted with a group selected from hydroxyl; thiol group; nitro group; cyano group; a halogen atom such as fluorine, chlorine, bromine and iodine; a C1-C8 alkyl group such as methyl, ethyl, n-propyl and isopropyl; C1-C8 alkoxy group such as methoxy, ethoxy, n-propoxy, isopropoxy and butoxy; halogenated alkyl group such as fluoromethyl group, difluoromethyl group, trifluoromethyl group and 2,2,2-trifluoroethyl group; alkyl thio group such as methyl thio group, ethyl thio group and isopropyl thio group; acyl group such as acetyl group, propionyl group and benzoyl group; hydroxyalkyl group such as hydroxymethyl group, hydroxyethyl group and hydroxypropyl group; amino group; monoalkyl amino group such as methyl amino group, ethyl amino group and isopropyl amino group; dialkyl amino group such as dimethyl amino group and diethyl amino group; cyclic amino group such as aziridinyl group, azetidinyl group, pyrrolidinyl group, piperidinyl group, perhydroazepinyl group and piperazinyl group; carboxyl; alkoxycarbonyl group such as methoxycarbonyl group, ethoxycarbonyl group and propylcarbonyl group; carbamoyl group; alkyl carbamoyl group such as methyl carbamoyl group and dimethyl carbamoyl group; acyl amino group such as acetyl amino group and benzoyl amino group; unsubstituted sulfamoyl or sulfamoyl substituted with a C1-C4 alkyl group; alkyl sulfonyl group such as methyl sulfonyl group and ethyl sulfonyl group; unsubstituted or substituted aryl sulfonyl group such as benzene sulfonyl group and p-toluene sulfonyl group; unsubstituted or substituted aryl group such as phenyl group, tolyl group and anisolyl group; unsubstituted or substituted heteroaryl group such as pyrrole group, pyrazolyl group, imidazolyl group, triazolyl group, tetrazolyl group, thiazolyl group, pyridyl group, pyrimidyl group and pyrazinyl group; carboxyalkyl group; alkyloxycarbonyl alkyl group such as methoxycarbonyl methyl group, ethoxycarbonyl methyl group and methoxycarbonyl ethyl group; carboxyalkoxy group such as carboxymethoxy group; aryl alkyl group such as benzyl group and 4-chlorobenzyl group; heteroaryl alkyl group such as pyridyl methyl group and pyridyl ethyl group; alkylene dioxy group such as methylene dioxy group and ethylene dioxy group; and oxo group.

[0017] The halogen atom in the definition of R^2 and R^3 means fluorine, chlorine, bromine and iodine.

[0018] The C1-C4, C1-C6 or C1-C8 alkyl group in the definition of R^1, R^2 and R^3 means a linear or branched alkyl group having 1-4, 1-6 or 1-8 carbon atoms, respectively. Examples thereof include methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, isobutyl group, sec-butyl group, t-butyl group, n-pentyl group, 1,2-dimethyl propyl group, 1,1-dimethyl propyl group, 2,2-dimethyl propyl group, 2-ethyl propyl group, n-hexyl group, 1,2-dimethyl butyl group, 2,3-dimethyl butyl group, 1,3-dimethyl butyl group, 1-ethyl-2-methyl propyl group, 1-methyl-2-ethyl propyl group, n-heptyl group, 1,1-dimethyl pentyl group, 2-ethyl pentyl group, 1-methyl-2-ethyl butyl group, n-octyl group, 1,1-dimethyl hexyl group, 2-ethyl hexyl group, 1-methyl-2-ethyl pentyl group etc.

[0019] The cycloalkyl group in the definition of R^1, R^2 and R^3 means C_{3-8} cycloalkyl group such as cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group, cycloheptyl group or cycloctyl group.

[0020] The C3-C6 cycloalkyl-C1-C4 alkyl group in the definition of R^3 means a group having C_{3-6} cycloalkyl group such as cyclopropyl group, cyclobutyl group, cyclopentyl group or cyclohexyl group bound to the above-mentioned C1-C4 alkyl group.

[0021] In the definition of and R^3, the C2-C8 alkenyl group and a linear or branched alkenyl group include e.g. 1-propenyl group, 2-propenyl group, isopropenyl group, 2-methyl-1-propenyl group, 3-methyl-1-propenyl group, 2-methyl-2-propenyl group, 3-methyl-2-propenyl group, 1-butenyl group, 2- butenyl group, 3- butenyl group etc.

[0022] In the optionally protected carboxyl group in the definition of R^3, the protective group includes e.g. C1-C8 alkyl group such as methyl group, ethyl group and tert-butyl group; C1-C8 alkyl group substituted with an optionally substituted phenyl group such as p-methoxybenzyl, p-nitrobenzyl, 3,4-dimethoxybenzyl, diphenylmethyl, trityl and phenetyl; halogenated C1-C8 alkyl group such as 2,2,2-trichloroethyl and 2-iodoethyl; C1-C8 alkanoyloxy C1-C8 alkyl group such as pivaloyloxymethyl, acetoxymethyl, propionyloxymethyl, butyryloxymethyl, valeryloxymethyl, 1-acetoxyethyl, 2-acetoxyethyl, 1-pivaloyloxyethyl and 2-pivaloyloxyethyl; higher alkanoyloxy C1-C8 alkyl group such as palmitoyloxyethyl, heptadecanoyloxymethyl and 1-palmitoyloxyethyl; C1-C8 alkoxycarbonyloxy C1-C8 alkyl group such as methoxycarbonyloxymethyl, 1-butoxycarbonyloxyethyl and 1-(isopropoxycarbonyloxy)ethyl; carboxy C1-C8 alkyl group such as carboxymethyl and 2-carboxyethyl; heteroaryl group such as 3-phthalidyl group; an optionally substituted benzoyloxy C1-C8 alkyl group such as 4-glycyloxybenzoyloxymethyl; (substituted dioxolene) C1-C8 alkyl group such as (5-methyl-2-oxo-1,3-dioxolene-4-yl)methyl; cycloalkyl substituted C1-C8 alkanoyloxy C1-C8 alkyl group such as 1-cyclohexylacetyloxyethyl; and cycloalkyloxycarbonyloxy C1-C8 alkyl group such as 1-cyclohexyloxycarbonyloxyethyl. Further, the substituent group may be various acid amides. In short, any groups which may be degraded in vivo by some means to form carboxylic acids can be used as the protective group for the carboxyl group.

[0023] Q and W are the same as or different from each other and are both N or one is N and the other CH.

[0024] R^1 represents hydrogen, atom or formula $-NR^4R^5$ (wherein R^4 and R^5 are the same as or different from each other and each represents hydrogen, a C1-C8 alkyl group or a C3-C8 cycloalkyl group, formula $-NR^4R^5$ (wherein R^4 and R^5 are the same as or different from each other and each represents hydrogen, a C1-C8 alkyl group, or a C3-C8 cycloalkyl group.

[0025] R^2 represents 1) hydrogen, 2) a halogen atom, 3) a C2 - C8 alkynyl group which may be substituted with a hydroxy or a C3-C6 cycloalkyl group, 4) a C1-C8 alkyl group or 5) a C1 - C8 alkoxy group preferably 1) hydrogen, 3) a C2-C8 alkynyl group which may be substituted with a hydroxyl, or a C3-C6 cycloalkyl group, 4) a C1-C8 alkyl group or 5) a C1-C8 alkoxy group more preferably 1) hydrogen, 3) a C2-C8 alkynyl group or 4) a C1-C8 alkyl group still more preferably 1) hydrogen or 4) a C1-C8 alkyl group , and most preferably hydrogen.

[0026] R^3 represents a 1,2-dihydro-2-oxopyridyl group which may be substituted with a) a halogen atom or a C1-C6 alkyl group and whose nitrogen atom may further be substituted with b-1) a C1-C6 alkyl group which may be substituted with a halogen atom, hydroxyl phenyl, C2-C8 alkenyl or an optionally protected carboxyl group, b-2) an optionally substituted C3-C6 cycloalkyl-C1-C4 alkyl group or b-3) an optionally substituted C3-C6 cycloalkyl group, more preferably a 1,2-dihydro-2-oxopyridyl group which may be substituted with a) a halogen atom or a C1-C6 alkyl group and whose nitrogen atom may further be substituted with b-1) a C1-C6 alkyl group which may be substituted with a halogen atom, hydroxyl or an optionally protected carboxyl group, and most preferably 1,2-dihydro-2-oxopyridyl group or 1-methyl-1,2-dihydro-2-oxopyridyl group.

[0027] In this case, when R^2 is i) a C2-C8 alkynyl group which may be substituted with a hydroxyl group or C3-C6 cycloalkyl group or ii) a C1-C8 alkyl group R^3 represents preferably a 1,2-dihydro-2-oxopyridyl group which may be substituted with a) a halogen atom or a C1-C6 alkyl group, and whose nitrogen atom may further be substituted with b-1) a C1-C6 alkyl group which may be substituted with a halogen atom, hydroxyl, phenyl, C2-C8 alkenyl or an optionally protected carboxyl group, b-2) an optionally substituted C3-C6 cycloalkyl-Cl-C4 alkyl group or b-3) an optionally substituted C3-C6 cycloalkyl group, further preferably) a 1,2-dihydro-2-oxopyridyl group which may be substituted with a) a halogen atom or a C1-C6 alkyl group and whose nitrogen atom may further be substituted with b-1) a C1-C6 alkyl group which may be substituted with a halogen atom, hydroxyl or an optionally protected carboxyl group, and most preferably a 1,2-dihydro-2-oxopyridyl group or a 1-methyl-1,2-dihydro-2-oxopyridyl group.

[0028] Ar represents 1) an optionally substituted phenyl group, 2) an optionally substituted pyridyl group, 3) an optionally substituted furyl group or 4) an optionally substituted thienyl more preferably 1) an optionally substituted phenyl group, 2) an optionally substituted pyridyl group or 3) an optionally substituted furyl group further preferably 1) an optionally substituted phenyl group or 2) an optionally substituted pyridyl group, and most preferably an optionally substituted phenyl group.

[0029] It goes without saying that when the compounds of the present invention have an asymmetric atom, optically active isomers thereof also fall under the scope of the present invention. Further, the present invention encompasses hydrates.

[0030] In the present invention, the pharmacologically acceptable salts include e.g. inorganic salts such as hydro-

chloride, hydrobromate, sulfate, and phosphate; organic acid salts such as acetate, maleate, tartrate, methanesulfonate, benzene sulfonate and toluene sulfonate, or salts with amino acids such as aspartic acid and glutamic acid.

[0031] The compound group of the present invention is also useful because of low toxicity and high safety.

[0032] When the compound of the present invention is used to treat the diseases described above, it can be administered orally or parenterally. The compound of the present invention can be administered in the form of tablets, powder, granules, capsules, syrups, troches, inhalations, suppositories, injections, ointments, eye ointments, eye drops, nose drops, ear drops, poultices and lotions.

[0033] Although the dose is significantly varied depending on the type of disease, the severeness of symptoms, the age and sex, the sensitivity to the chemical of a patient, the present compound is administered in one portion or divided portions in a daily dose of usually about 0.03 to 1000 mg, preferably 0.1 to 500 mg, more preferably 0.1 to 100 mg. The dose of the injection is usually about 1 μg/kg to 3000 μg/kg, preferably about 3 μg/kg to 1000 Pg/kg.

[0034] The compound of the present invention can be formed into a pharmaceutical preparation in a usual manner by using usual pharmaceutical carriers.

[0035] That is, when the oral solid pharmaceutical preparation is to be prepared, excipients as the major ingredient, a binder, a disintegrating agent, a lubricant, a coloring agent, flavoring agent, and an antioxidant are added to the compound of the present invention and formed in a usual manner into tablets, coated tablets, granules, powder, capsules etc.

[0036] The fillers include e.g. lactose, corn starch, white sugar, glucose, sorbitol, crystalline cellulose, silicon dioxide etc.

[0037] The binder includes e.g. polyvinyl alcohol, polyvinyl ether, ethyl cellulose, methyl cellulose, gum arabic, tragacanth, gelatin, shellac, hydroxy propyl cellulose, hydroxy propyl methyl cellulose, calcium citrate, dextrin, pectin etc., and the lubricant includes e.g. magnesium stearate, talc, polyethylene glycol, silica, hardened vegetable oil etc.

[0038] The coloring agent includes e.g. those coloring agents approved to be added to pharmaceutical preparations, and the flavoring agent include cocoa powder, menthol, aromatic powder, peppermint oil, borneol, cinnamon powder etc. The antioxidant includes ascorbic acid, α-tocopherol etc. which are approved to be added to pharmaceutical preparations. The tablets and granules may be coated as necessary with sugar coating, gelatin coating etc.

[0039] On the other hand, when the injection preparation, eye drops etc. are to be produced, a pH adjuster, a buffer, a suspension agent, a solubilizer, a stabilizer, an isotonizing agent, an antioxidant, a preservative etc. may be added to the major chemical and formed in a usual manner into the preparation. If necessary, the preparation can be formed into a freeze-dried preparation. The injection can be administered intravenously, subcutaneously or intramuscularly.

[0040] Examples of the suspension agent include methyl cellulose, Polysorbate 80, hydroxyethyl cellulose, gum arabic, tragacanth powder, sodium carboxymethyl cellulose and polyoxyethylene sorbitan monolaurate.

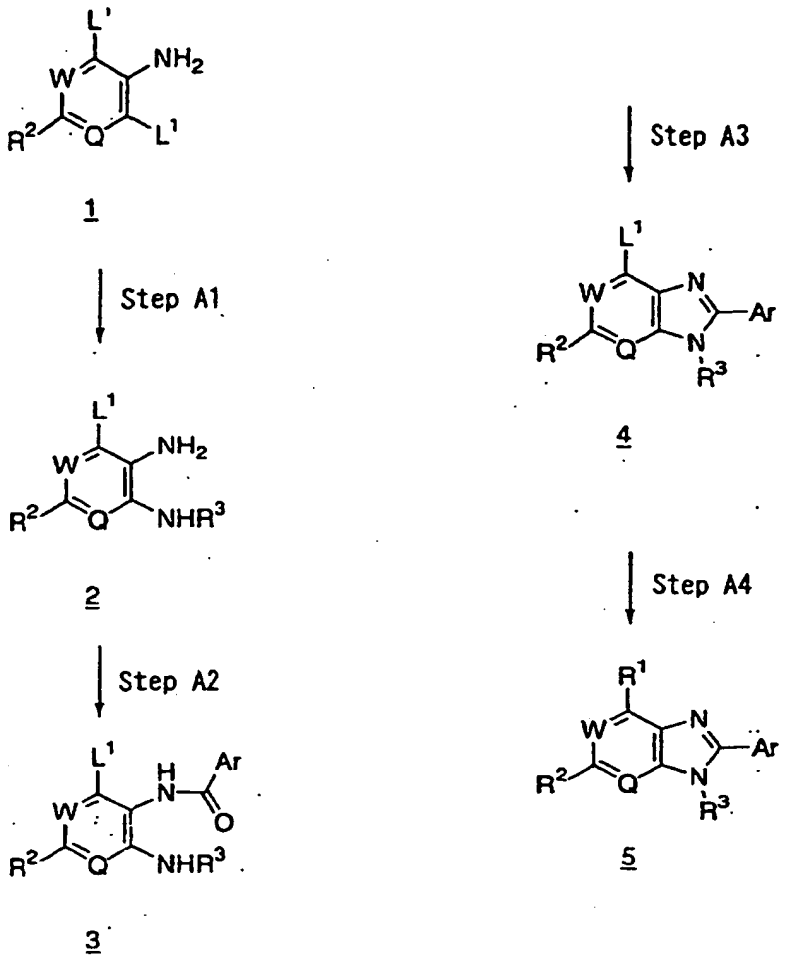
[0041] The solubilizer includes polyoxyethylene hardened castor oil, Polysorbate 80, nicotinic acid amide, polyoxyethylene sorbitan monolaulate.

[0042] The stabilizer includes e.g. sodium sulfite, sodium metasulfite and ether, and the preservative includes e.g. methyl p-oxybenzoate, ethyl p-oxybenzoate, sorbic acid, phenol, cresol, chlorocresol etc.

[0043] When the ointment is to be produced, the preparation can be produced in a usual manner by adding a stabilizer, an antioxidant and a preservative as necessary.

[0044] The novel purine compound of the present invention can be produced by combination of generally known methods. Hereinafter, the major conventional method of producing the compound group of the present invention is described.

Production method A



wherein L^1 means a halogen atom, and R^1, R^2, R^3, Ar, Q and W have the same meanings as defined above.

Step A1: This step is the step of allowing a compound 5-amino-4,6-dihalogeno-2-pyrimidine 1 synthesized in accordance with a known method to react in a solvent with various primary amine compounds to replace a halogen atom at the 4-position by the amine derivatives, to produce 4,5-diaminopyrimidine derivative 2.

[0045] The reaction is carried out using an amine in excess, or in the presence of a tertiary amine such as triethylamine and diisopropyl ethylamine when the amine reacted is an alkyl amine, alkynyl amine and allyl amine, or in the presence of a catalytic amount of mineral acid, preferably with the coexistence of hydrochloric acid when the amine reacted is an aryl amine or heteroaryl amine. However, the reaction may be carried out in the absence of hydrochloric acid using carboxylate thereof.

[0046] The solvent used is not particularly limited insofar as the reaction is not inhibited and the starting material is dissolved to a certain extent, and preferable examples include NMP (1-methyl-2-pyrrolidone); ethers such as tetrahydrofuran, dioxane, dimethoxyethane and diethylene glycol dimethyl ether; halogenated hydrocarbons such as methylene chloride, chloroform and dichloroethane. When the amine reacted is an aryl amine or heteroaryl amine, a mixed solvent of alcohol and water can be used. The reaction temperature is varied depending on the reactivity of the amine derivative used, preferably from room temperature to the boiling point of each solvent, more preferably a temperature at which the reaction solution is refluxed.

Step A2: This step is the step of reacting ArCOX (wherein X is a halogen atom; and Ar has the same meaning as defined above) with 4,5-diaminopyrimidine derivative 2, to produce 5-acylaminopyrimidine derivative 3.

[0047] This reaction is carried out at a temperature ranging from 0°C to room temperature in pyridine or in the presence of a base in a solvent not participating in the reaction such as methylene chloride, chloroform, ethyl acetate, tetrahydrofuran, dioxane, dimethoxyethane, benzene and toluene.

Step A3: This step is the step of dehydration condensation of the acyl amino group with its adjacent substituted amino group on the pyrimidine ring to form an imidazole ring, thus producing purine derivative 4.

[0048] The reaction is carried out under reflux in phosphorus oxychloride. The reaction can also be conducted in the presence of hydrochloric acid. Further, the reaction can also be conduced under heating in NMP.

[0049] The steps A2 and A3 can also proceed in one-pot reaction.

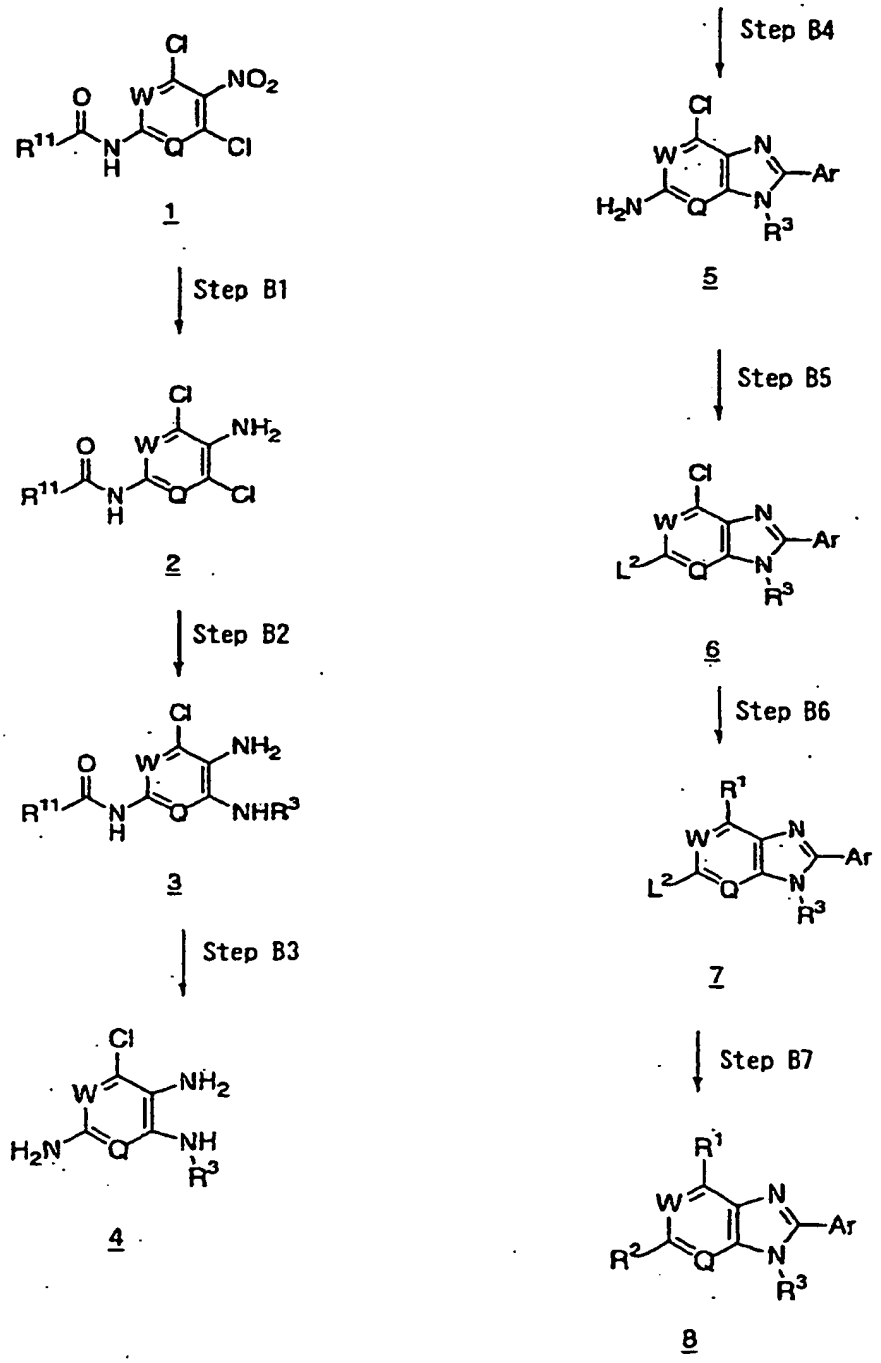
Step A4 : This step is the step of allowing a halogen atom at the 6-position in the purine derivative 4 to react with an amine derivative, to produce 6-amino-8,9-di-substituted purine derivative 5.

[0050] When the amine derivative is gas or has a low boiling point, the reaction is carried out preferably in a sealed tube or in an autoclave.

[0051] The solvent used is not particularly limited insofar as the reaction is not inhibited and the starting material is dissolved to a certain extent, and preferable examples include alcohols such as methanol and ethanol; ethers such as tetrahydrofuran, dioxane, dimethoxyethane and diethylene glycol dimethyl ether; halogenated hydrocarbons such as methylene chloride, chloroform and dichloroethane; dimethylformamide, 1-methyl pyrrolidinone etc.

[0052] The reaction temperature is preferably 0 to 150 °C, more preferably 50 to 100 °C.

Production method B



wherein L^2, R^1, R^2, R^3, Ar, Q and W have the same meanings as defined above; and R^{11} means a C1-C4 alkyl group.

Step B1: This step is the step of subjecting the nitro group in 2-acylamino-4,6-dichloro-5-nitropyrimidine derivative 1 produced in a known method to catalytic reduction, reduction with a metal or a metal salt, or reduction with a metal hydride, to produce 2-acylamino-5-amino-4,6-dichloropyrimidine derivative 2.

[0053] The catalytic reduction is conducted at normal pressure or under pressure, at room temperature or under heating, in the presence of a catalyst such as Raney Ni, Pd-C or PtO_2 in a hydrogen atmosphere. It is conducted

preferably at normal pressure and at ordinary temperature, more preferably in the presence of Raney Ni as the catalyst at normal pressure and at ordinary temperature. The solvent used is not particularly limited insofar as it dissolves the starting material to a certain extent without causing catalytic poison, and preferable examples include methanol, ethanol, tetrahydrofuran, dioxane, acetic acid, dimethylformamide or a mixed solvent thereof. The reduction with a metal or a metal salt is conducted using zinc powder-hydrochloric acid, stannous chloride-hydrochloric acid, or iron-hydrochloric acid in an alcohol such as hydrous or anhydrous methanol or ethanol or in dioxane or tetrahydrofuran as the solvent. The reduction with a metal hydride is conducted using Pd-sodium borohydride, $NiCl_2(PPh_3)_2$-sodium borohydride, or stannous chloride-sodium borohydride in a methanol, ethanol or tetrahydrofuran solvent.

Step B2: This step is the step of allowing the 2-acylamino-5-amino-4,6-dichloropyrimidine derivative 2 to react with a primary amine derivative to replace the chlorine atom at the 4-position by the amino derivative, to produce 4,5-diaminopyrimidine derivative 3.

[0054] This reaction is carried out preferably using an amine in excess, or in the presence of a tertiary amine such as triethylamine or diisopropyl ethylamine when the amine reacted is an alkyl amine, alkynyl amine and allyl amine, or in the presence of a catalytic amount of mineral acid, particularly hydrochloric acid when the amine reacted is an aryl amine or heteroaryl amine.

[0055] The solvent used is not particularly limited insofar as the reaction is not inhibited and the starting material is dissolved to a certain extent, and:preferable examples include ethers such as tetrahydrofuran, dioxane, dimethoxyethane and diethylene glycol dimethyl ether; and halogenated hydrocarbons such as methylene chloride, chloroform and dichloroethane. The reaction temperature varies depending on the reactivity of the amine derivative used, preferably from room temperature to reflux temperature, more preferably reflux temperature.

Step B3: This step is the step of eliminating the acyl group i.e. a protective group for the amino group at the 2-position in the 2-acylaminopyrimidine derivative 3, to produce 2-aminopyrimidine derivative 4.

[0056] The reaction is carried out by reacting with an aqueous mineral acid or alkaline solution in a solvent such as methanol, ethanol, dioxane or tetrahydrofuran. The reaction also proceeds at room temperature, but is carried out preferably under heating.

[0057] This step can be finished in the previous step B2 depending on the conditions for substitution with the amino derivative in the step B2, and in such case, this step is omitted.

Step B4: This step is the step of dehydration condensation of the amino group at the 4-position with its adjacent aldehyde at the 5-position on the pyrimidine ring to form an imidazole ring thereby producing a purine derivative 5.

[0058] The reaction is carried out by condensing the amino group at the 5-position with the aldehyde derivative to form a Schiff base, followed by ring closure by reaction with ferric chloride etc.

[0059] The solvent used is not particularly limited insofar as the reaction is not inhibited and the starting material is dissolved to a certain extent, and preferable examples include alcohols such as methanol and ethanol, ethers such as tetrahydrofuran, dioxane, dimethoxyethane, and diethylene glycol dimethyl ether, and dimethylformamide. The reaction is conducted at 0 to 100 °C, preferably at room temperature. For production of the Schiff base, acetic acid is preferably added.

Step B5: This step is the step of converting the amino group in the 2-aminopurine derivative 6 by the Sandmeyer reaction into a halogen atom to produce 2,6-dihalogenopurine derivative 6.

[0060] The reaction is carried out by converting the amino group into a diazonium group by diazo reaction with a nitrite such as sodium nitrite, amyl nitrite or isoamyl nitrite and then converting the diazonium group into a halogen atom by cuprous halide. In the diazo reaction, an acid is not particularly necessary when a nitrite such as isoamyl nitrite is used, and the amino group can be converted into a halogen atom under heating by adding cuprous halide and methylene halide to a solvent such as dioxane or tetrahydrofuran. In the present invention, it is most preferable that cuprous iodide is used as cuprous halide and diiodomethane is used as methylene halide, to produce the 2-iodopurine derivative by conversion.

Step B6: This step is the step of allowing the chlorine atom at the 6-position in the 6-chloro-2-iodopurine derivative 6 to react with an amine derivative to produce 6-amino-2-iodopurine derivative 8.

[0061] When the amine derivative is gas or has a low boiling point, the reaction is carried out preferably in a sealed tube or in an autoclave.

[0062] The solvent used is not particularly limited insofar as the reaction is not inhibited and the starting material is dissolved to a certain extent, and preferable examples include alcohols such as methanol and ethanol; ethers such as tetrahydrofuran, dioxane, dimethoxyethane and diethylene glycol dimethyl ether; halogenated hydrocarbons such as methylene chloride, chloroform and dichloroethane; and dimethylformamide, 1-methyl pyrrolidinone etc.

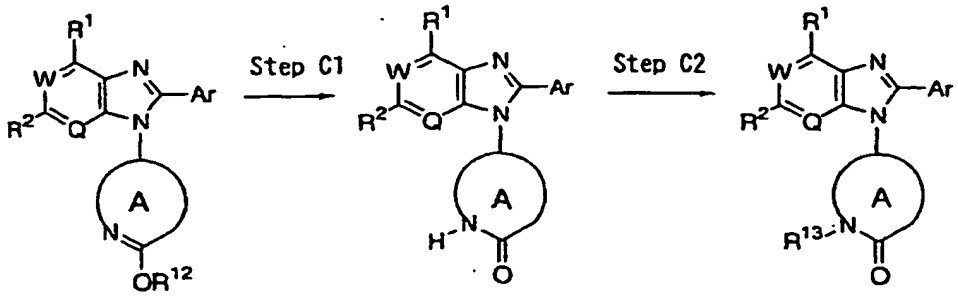
[0063] The reaction temperature is preferably 0 to 150°C, more preferably 50 to 100°C.

Step B7: This step is the step of selectively subjecting the halogen atom at the 2-position in the 2-halogenopurine derivative 7 to coupling reaction with an ethynyl side chain, to produce 2-ethylnylene-6-halogenopurine derivative 8.

[0064] The reaction is conducted at room temperature or under heating in the presence of a catalytic amount of dichlorobisphenyl phosphine palladium (II), cuprous iodide and a tertiary amine. The solvent used includes ethers such

as tetrahydrofuran, dioxane, dimethoxyethane and diethylene glycol dimethyl ether, dimethylformamide, 1-methyl pyrrolidinone etc. The tertiary amine used includes triethylamine, diisopropylamine, DBU, dimethyl aniline etc. The reaction temperature is preferably 0 to 100°C, more preferably room temperature.

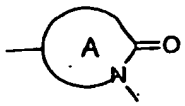
Production method C



1 2 3

wherein R^1, R^2, Ar, Q and W have the same meanings as defined above; R^{12} is a C1-C8 alkyl group; R^{13} is a C1-C6 alkyl group which may be substituted with a halogen atom, hydroxyl or an optionally protected carboxyl group, an optionally substituted C3-C6 cycloalkyl-C1-C4 alkyl group or an optionally substituted C3-C6 cycloalkyl group; the formula:

means a pyridinyl group, pyrimidyl group or pyrazinyl group; and the formula:



means a dihydroxopyridinyl or -pyrimidyl group, or dihydro- or tetrahydropyranydinyl group.

[0065] This production method C is a method of hydrolyzing the alkoxy group in the α-alkoxy N-containing heteroaryl compound in R^3 obtained in production method A or B, to produce an α-hydroxy N-containing heteroaryl derivative or to introduce a substituent group into the nitrogen atom in the ring.

Step C1: This step is the step of hydrolyzing the alkoxy group in the 9-α-alkoxy N-containing heteroaryl purine derivative 1, to produce 9-α-hydroxy N-containing heteroaryl purine derivative 2.

[0066] The reaction is carried out at room temperature to 100 °C in the presence of an aqueous solution of mineral acid such as hydrochloric acid, hydrobromic acid, sulfuric acid etc.

Step C2: This step is the step of introducing a substituent group into the nitrogen atom in the 9-α-hydroxy N-containing heteroaryl purine derivative 2 obtained above.

[0067] The reaction is carried out in the presence of a base by reaction with a halogenated alkyl compound, a halogenated fluoroalkyl compound, an alkoxycarbonyl alkyl halogen compound and various sulfonate compounds in a solvent.

[0068] The base includes sodium hydride, sodium hydroxide, potassium hydroxide, sodium bicarbonate, sodium carbonate, potassium carbonate or sodium alkoxide, and the solvent includes alcohols such as methanol and ethanol; ethers such as tetrahydrofuran, dioxane, dimethoxyethane and diethylene glycol dimethyl ether; halogenated hydrocarbons such as methylene chloride, chloroform and dichloroethane; and N,N--dimethylformamide, dimethylsulfoxide,

1-methyl pyrrolidinone etc. The reaction is carried out at a temperature of 0 to 100°C.

Production method D

1 2

wherein $R^{2''}$ means a C1-C8 alkoxy group; and R^1, R^3, L^2, Ar, Q and W have the same meanings as defined above.

[0069] The production method D is a method of converting the halogen atom at the 2-position in the compound 7 obtained in the production method B into a C1-C8 alkoxy group.

[0070] This reaction proceeds even if L^2 is any halogen atom, but bromine is preferable. By treatment with a hydrobromic acid solution, the iodine-atom derivative is easily converted into a bromine derivative.

[0071] The reaction is carried out by reacting with sodium or potassium alkoxide.

Production method E

1 2

wherein R^8 means a C1-C4 alkyl group; and R^1, R^3, Ar, Q and W have the same meanings as defined above.

[0072] This production method is a method of subjecting the ethynylene group in the compound 8 obtained in the production method B to catalytic reduction, to give an alkyl derivative.

[0073] The catalytic reduction is conducted at normal pressure or under pressure, at room temperature or under heating, in the presence of a catalyst such as Raney Ni, Pd-C or PtO_2 in a hydrogen atmosphere. It is conducted preferably at normal pressure and at ordinary temperature, more preferably in the presence of Raney Ni as the catalyst at normal pressure and at ordinary temperature. The solvent used is not particularly limited insofar as it dissolves the starting material to a certain extent without causing catalytic poison, and preferable examples include methanol, ethanol, tetrahydrofuran, dioxane, acetic acid, dimethylformamide or a mixed solvent thereof.

[0074] Hereinafter, pharmacological experiments will be shown to explain the excellent effect of the purine compounds of the present invention.

Effect of Novel Purine Compounds

1) Adenosine A2a receptor binding assay

[0075] A membrane specimen prepared by over-expression of adenosine A2a receptor was purchased from Receptor Biology Inc., and used to carry out adenosine A2a receptor binding assays. The purchased membrane specimen was suspended at a concentration of 22. 2 μg/ml in an incubation buffer (20 mM HEPES, 10 mM $MgCl_2$ and 100 mM NaCl, pH 7.4). To 0.45 ml of this membrane specimen were added 0.025 ml of tritium-labeled ^{3}H-CGS21680 (500 nM; 30 Ci/mmol) and 0.025 ml of the test compound. The solution of the test compound was prepared by dissolving the compound at a concentration of 20 mM in DMSO and then successively diluting the solution 10-fold with the incubation buffer. The mixture was allowed to stand at 25 °C for 90 minutes, subjected to quick suction on a glass fiber filter (GF/B; manufactured by Whatman) and immediately washed twice with 5 ml of ice-cooled 50 mM Tris-HCl buffer. Thereafter,

the glass fiber filter was transferred to a vial bottle, a scintillator was added thereto, and the radioactivity on the filter was measured by a liquid scintillation counter. The rate of inhibition of (^{3}H-CGS21680) binding to the A2a receptor by the test compound was calculated using the following equation, and from this rate of inhibition, IC_{50} was calculated.

Rate of inhibition (%)=[1-{(Binding amount in the presence of drug-non-specific binding amount)/(Total binding amount-Non - specific binding amount)}]$^{\times}$100

[0076] The total binding amount is ^{3}H-CGS21680 binding radioactivity in the absence of the test compound. The non-specific binding amount is ^{3}H-CGS21680 binding radioactivity in the presence of 100 μM of RPIA. The binding amount in the presence of drug is ^{3}H-CGS21680 binding radioactivity in the presence of the test compound of various concentrations.

[0077] The inhibition constant (Ki value) was calculated from Cheng-Prusoff's expression.

[0078] The inhibition constant (Ki value) of the compound in Example 4 was 0.0032.

2) Inhibitory effect of test compound on NECA-stimulate cAMP production in adenosine A2b receptor-expressing cells

[0079] Human adenosine A2b receptor cDNA was over-expressed in CHOK1 cells. The cells were uniformly placed on a 24-well plate at a density of 1.5×10^5 cells/well, incubated overnight and then used for the assays. Affinity of the test compound for the A2b receptor was evaluated by using, as an index, the rate of suppression of the amount of cAMP produced by stimulation of an adenosine agonist NECA (30 nM) in the presence of the test compound. Thus, the plate was washed twice with 2 ml/well of Krebs-Ringer-Bicarbonate buffer (KRB) (mM) (NaCl 118, KCl 4.8, KH_2PO_4 1.2, $MgSO_4$ 1.2, $CaCl_2$ 3.4, HEPES 10, $NaHCO_3$ 25, pH 7.4) and then pre-incubated (0.5 ml/well) for 30 minutes. Thereafter, a mixed solution containing 600 μM Ro-20-1724 (phosphodiesterase inhibitor), 180 nM NECA, and a test compound at a concentration 6-times higher than in the reaction solution was added in an amount of 100 μm/well . After 15 minutes, the reaction was stopped by replacing the reaction solution by 0.1 N HCl (300 μl/well). Measurement of cAMP was carried out using an Amersham cAMP EIA Kit.

[0080] The rate of inhibition of NECA-stimulated cAMP production by the test compound was calculated using the following equation:

Rate of Inhibition (%) =[1-{(cAMP amount in the presence of NECA and test compound-Basal cAMP amount)/(cAMP amount stimulated only by NECA-Basal cAMP amount)}]×100.

[0081] IC_{50} was calculated from the rate of inhibition.

[0082] The IC_{50} of the compound in Example 4 was 0.011 μM.

3) Inhibitory action of test compound on NECA-stimulated glucose production in primary cultured rat hepatic cells

[0083] Hepatic cells were separated by a collagenase perfusion method from livers of male rats of Wistar strain and subjected to a primary culture in a William's Medium E containing 5 % calf serum, 10^{-6} M insulin and 10^{-7} M dexamethasone. After 1 day, the hepatic cells were washed with a Krebs-Ringer Bicarbonate buffer (mM) (NaCl 118, KCl 4.8, KH_2PO_4 1.2, $MgSO_4$ 1.2, $CaCl_2$ 3.4, HEPES 10, $NaHCO_3$ 25) pH 7.4 (KRB) containing 10 mM HEPES and 0.1 % bovine serum albumin and KRB was added thereto, then incubated at 37 °C. After 30 minutes, NECA (N-ethylcarboxamide adenosine) (final concentration: 0.1 μM) and a test compound were added thereto at the same time, the mixture was incubated for additional one hour, and the amount of glucose released into the incubation medium was measured.

[0084] IC_{50} value (μM) for inhibition of NECA-stimulated glucose release by the compound in Example 4 was 0.0076.

4) Action of test compound on hyperglycemia in spontaneously diabetic mice (KK-Ay/Ta Jcl) (single administration)

[0085]

Animals: Seven male KK-Ay/Ta Jcl mice for each group (purchased from Nippon Clair)
Preparation and Administration of Test Compound: A test compound in a dose as shown in Table 1 was suspended in 0.5 % aqueous methyl cellulose solution and was orally administered in a volume of 10 ml/kg.
Collection of Blood Samples and Determination of Blood Sugar: Blood was collected from tail veins just before administration of the test compound and also 5 hours after the administration and blood sugar was determined.
Method: Tail vein of a mouse was injured by a razor without anesthetization to bleed slightly. The blood (15 µl) was collected and immediately mixed with 135 µl of 0.6 M perchloric acid. Glucose in the supernatant separated by centrifugation (at 1500 g for 10 minutes at 4°C using a cooling centrifuge GS-6KR from Beckmann) was determined by Glucose CII Test Wako (Wako Pure Chemicals).

[0086] The results are shown in Table 1.

[0087] The results are shown in terms of "(% ratio of blood sugar 5 hours after the administration to the blood sugar before the administration) ± (standard error)". The data were subjected to one-way layout analysis of variance and then subjected to multiple comparison of Dunnett type. Difference with $p<0.05$ was deemed significant.

Table 1

Action of test compound on hyperglycemia in spontaneously diabetic mice (KK-Ay/Ta Jcl)			
Test Compound	Dose (mg/kg)	$\frac{\text{Blood sugar level 5hr after the administration}}{\text{Blood sugar level just before the administration}} \times 100$ (%)	Statistical significance
Control		72.5 ± 3.7	
Example 4	10	47.3 ± 7.2	**

(** p<0.01 vs. control)

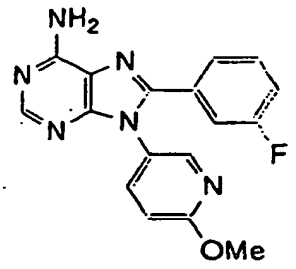
[0088] As described above, the compound of the present invention had an adenosine A2 receptor antagonism and showed a clear effect on the pathological models of diabetes mellitus. In addition, the compound of the present invention also showed an improving action in investigation for impaired glucose tolerance in a glucose tolerance test, and was confirmed to act not only in the liver but also in the peripheral tissues.

Examples

[0089] Hereinafter, the processes for synthesizing the novel purine compounds of the present invention are exemplified, but as a matter of course, these Examples are shown for the purpose of facilitating the understanding of the present invention and not intended to limit the present invention.

Comparative example 1: 8-(3-fluorophenyl)-9-(6-methoxy-3-pyridyl)-9H-6-purineamine

[0090]



(1) Synthesis of N4-(6-methoxy-3-pyridyl)-6-chloro-4,5-pyrimidinediamine hydrochloride

[0091] 5-Amino-2-methoxypyridine (8.7 g, 70.1 mmol) and conc. hydrochloric acid (1.5 ml) were added successively to a suspension of 5-amino-4,6-dichloropyrimidine (10.0 g, 45.2 mmol, produced by Tokyo Kasei Co., Ltd.) in water (100 ml)/ethanol (15 ml) at room temperature, and the mixture was heated under reflux for 3 hours. After cooling as it was, the resulting solid was collected by filtration, washed with water and air-dried at 50°C, to give the title compound (6.6 g, 72 %) as a reddish brown solid.
^{1}H NMR (400 MHz, DMSO-d_6) δppm; 3.84 (3H, s), 6.84 (1H, d, J = 9.6 Hz), 7.82 (1H, s), 7.99 (1H, dd, J = 2.8, 9.6 Hz), 8.39 (1H, d, J = 2.8 Hz), 8.78 (1H, s).

(2) Synthesis of N1-[4-chloro-6-[(methoxy-3-pyridyl)amino]-5-pyrimidinyl]-3-fluorobenzamide

[0092] 3-Fluorobenzoyl chloride (9.6 ml, 79.0 mmol) was added dropwise over 80 minutes in a nitrogen atmosphere at 0 to 5 °C to a pyridine (66 ml) suspension of the compound (6.6 g, 22.9 mmol) obtained in (1), and the mixture was stirred as such for 5 hours. The reaction solution was diluted with water and ethyl acetate. The organic layer was washed with 1 N hydrochloric acid (×1). After the 1N hydrochloric acid layer was extracted with ethyl acetate (×2), the combined organic layers were washed with a saturated aqueous sodium bicarbonate solution (×1), dried over anhydrous sodium sulfate and concentrated. The residue was suspended in diethyl ether, and the solid was collected by filtration and washed with diethyl ether, to give the title compound (6.5 g, 76 %) as a colorless solid.
^{1}H NMR (400MHz, DMSO-d_6) δ ppm 3.84(3H, s), 6.84(1H, d, J=8.8Hz), 7.47-7.54 (1H, m), 7.59-7.66 (1H, m), 7.81-7.94 (3H, m), 8.26 (1H, d, J = 2.4 Hz), 8.33 (1H, s), 9.38(1H, s), 10.16 (1H, s).

(3) Synthesis of 6-chloro-8-(3-fluorophenyl)-9-(6-methoxy-3-pyridyl)-9H-purine

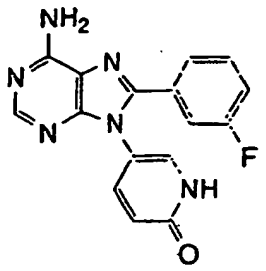
[0093] A suspension of the compound (435 mg, 1.16 mmol) obtained in (2) in phosphorus oxychloride (30 ml) was heated under reflux for 4.5 hours in a nitrogen atmosphere. After cooling as it was, the reaction solution was concentrated. The residue was diluted with ethyl acetate, washed with water (×3), a saturated aqueous sodium bicarbonate solution (×2) and brine (×1), dried over anhydrous sodium sulfate and concentrated. The residue was suspended in diethyl ether, and the solid was collected by filtration and washed with diethyl ether, to give the title compound (248 mg, 60 %) as a colorless solid.
^{1}H NMR (400MHz, DMSO-d_6) δ ppm 3.93(3H,s), 7.05(1H,d,J=8.8Hz), 7.38-7.48 (3H, m), 7.50-7.56 (1H, m), 7.90 (1H, dd, J=2.8,8.8Hz), 8.35 (1H, d, J = 2.8 Hz), 8.79 (1H, s).

(4) Synthesis of 8-(3-fluorophenyl)-9-(6-methoxy-3-pyridyl)-9H-6-purineamine

[0094] A suspension of the compound (1.0 g, 2.81 mmol) obtained in (3) in 1,2-dimethoxyethane (40 ml)/conc. ammonia water (20 ml) was stirred for 11 hours in an autoclave at 70 °C. After cooling as it was, the reaction solution was diluted with a saturated ammonium chloride solution and ethyl acetate. The organic layer was washed with a saturated aqueous ammonium chloride solution (×1), dried over anhydrous sodium sulfate and concentrated. The residue was suspended in diethyl ether, and the solid was collected by filtration and washed with diethyl ether, to give the title compound (928 mg, 98 %) as a colorless solid.
^{1}H NMR (400MHz, DMSO-d_6) δppm 3.91 (3H, s), 6. 99 (1H, d, J=8.8Hz), 7.26-7.33 (2H, m), 7.34-7.38 (1H, m), 7.43-7.49 (1H,m), 7.50 (2H, br s), 7.81 (1H, dd, J = 2.8, 8.8 Hz), 8.14 (1H,s), 8.23 (1H, d, J = 2.8 Hz)

Example 18: 5-[6-Amino-8-(3-fluorophenyl)-9H-9-purinyl]-1,2-dihydro-2-pyridinone

[0095]

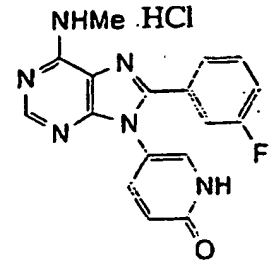


[0096] A suspension of 8-(3-fluorophenyl)-9-(6-methoxy-3-pyridyl)-9H-6-purineamine (890 mg, 2.65 mmol) obtained in Comparative example 1 in a conc. aqueous hydrobromic acid solution (12 ml) was stirred at 100 °C for 15 minutes. After cooling as it was, the reaction solution was neutralized with 5N aqueous sodium hydroxide solution, and the resulting solid was collected by filtration, washed with water, ethyl acetate and diethyl ether, to give the title compound (767 mg, 90 %) as a colorless solid. ^{1}H NMR (400 MHz, DMSO-d_6) δppm; 6.42 (1H, d, J = 9.2Hz), 7.29-7.36 (1H, m), 7.40-7.56 (6H, m), 7.70 (1H, d, J = 2.8 Hz), 8.15 (1H,s).

[0097] This compound (200 mg, 0.621 mmol) was dissolved in methanol-4N hydrochloric acid/ethyl acetate (10 drops) and concentrated. After the residue was crystallized from methanol/ethyl acetate/diethyl ether, the solid was collected by filtration and washed with diethyl ether, to give the hydrochloride (189 mg, 85 %) as a colorless solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm; 6.47 (1H, d, J = 9.6 Hz), 7.36-7.43 (1H, m), 7.44-7.60 (4H, m), 7.77 (1H, d, J = 2.8 Hz), 8.47 (1H, s). MS m/e (ESI) :323 (MH^+).

Example 2 5-[8-(3-Fluorophenyl)-6-(methylamino)-9H-9-purinyl]-1,2-dihydro-2-pyridinone hydrochloride

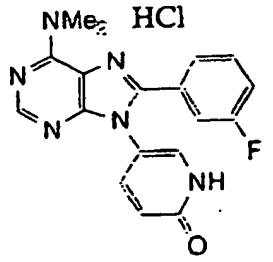
[0098]



[0099] Monomethylamine was used in place of ammonia in (4) in comparative example 1, and synthesis was carried out in the same manner as in example 1.
^{1}H NMR (400 MHz, DMSO-d_6) δppm; 3.10 (3H, br s), 6.47 (1H, d, J = 9.2 Hz), 7.34-7.42 (1H, m), 7.42-7.60 (4H, m), 7.76 (1H, d, J = 2.8 Hz), 8.41 (1H, s).
MS m/e (ESI) :337 (MH^+).

Example 3 5-[6-(Dimethylamino)-8-(3-fluorophenyl)-9H-9-purinyl]-1,2-dihydro-2-pyridinone hydrochloride

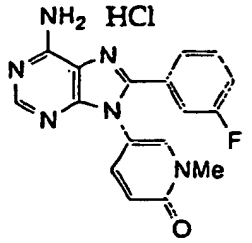
[0100]



[0101] Dimethylamine was used in place of ammonia in (4) in comparative example 1, and synthesis was carried out in the same manner as in example 1.
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm; 3.56 (6H, br s), 6.46 (1H, d, J = 9.2 Hz), 7.32-7.39 (1H, m), 7.42-7.57 (4H, m), 7.75 (1H, d, J = 2.8 Hz), 8.32 (1H, s).
MS m/e (ESI): 351 (MH^+).

Example 4 5-[6-Amino-8-(3-fluorophenyl)-9H-9-purinyl]-1-methyl-1,2-dihydro-2-pyridinone hydrochloride

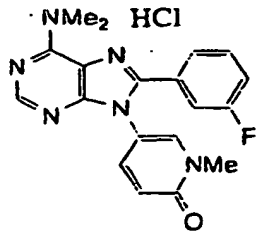
[0102]



[0103] N,N-Dimethylformamide dimethylacetal (0.5 ml, 3.76 mmol) was added to a suspension of 5-[6-amino-8-(3-fluorophenyl)-9 H-9-purinyl]-1,2-dihydro-2-pyridinone (1.0 g, 3.10 mmol) in Example 1 in N,N-dimethylformamide (10 ml) and stirred in a nitrogen atmosphere at room temperature. After 1 hour, N,N-dimethylformamide dimethyl acetal (0.5 ml, 3.76 mmol) was further added thereto and stirred for additional 1.5 hours. The reaction solution was ice-cooled, and 60 to 70 % sodium hydride (136 mg, 3.40 mmol) was added thereto at 0 to 6 °C and stirred. After 30 minutes, iodomethane (0.29 ml, 4.66 mmol) was added dropwise thereto and stirred. After 20 minutes, conc. ammonia water (10 ml) was added thereto and stirred at room temperature. After 16 hours, the reaction solution was diluted with a saturated aqueous ammonium chloride solution and ethyl acetate. The aqueous layer was extracted with ethyl acetate ($^{\times}$4), and the combined organic layers were washed with 1 N aqueous sodium hydroxide solution ($^{\times}$1) and a saturated aqueous ammonium chloride solution ($^{\times}$1), dried over anhydrous sodium sulfate and concentrated. The residue was suspended in ethyl acetate, and the solid was collected by filtration and washed with ethyl acetate, to give the title compound in free form (703 mg) . This free compound was dissolved in methanol-4N hydrochloric acid/ethyl acetate (1.5 ml) and concentrated. The residue was crystallized from methanol/ethyl acetate/diethyl ether, and the solid was collected by filtration and washed with diethyl ether, to give the title compound (697 mg, 60 %) as a colorless solid.
^{1}H NMR (400 MHz, DMSO-d_6) δppm; 3.46. (3H, s), 6.52 (1H, d, J = 9.2 Hz), 7.36-7.43 (1H, m), 7.44-7.60 (4H, m), 8.15 (1H, d, J = 2.8 Hz), 8.42 (1H, s).
MS m/e (ESI) :337 (MH^+).

Example 5 5-[6-(Dimethylamino)-8-(3-fluorophenyl)-9H-9-purinyl]-1-methyl-1,2-dihydro-2-pyridinone hydrochloride

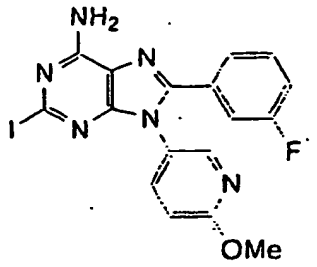
[0104]



[0105] 60 to 70 % sodium hydride (28 mg, 0.700 mmol) was added to a suspension of 5-[6-(dimethylamino)-8-(3-fluorophenyl)-9 H-9-purinyl]-1,2-dihydro-2-pyridinone hydrochloride (130 mg, 0.336 mmol) in Example 3 in N,N-dimethylformamide (3 ml), and the mixture was stirred in a nitrogen atmosphere at 0 to 6 °C. After 1 hour, iodomethane (23 µl, 0.369 mmol) was added thereto and stirred. After 30 minutes, 60 to 70 % sodium hydride (17 mg, 0.425 mmol) was added thereto, and 30 minutes thereafter, additional iodomethane (23 µl, 0.369 mmol) was added thereto and stirred. After 30 minutes, the reaction solution was diluted with a saturated aqueous ammonium chloride solution and ethyl acetate. The organic layer was washed with a saturated aqueous ammonium chloride solution (×1) and then extracted with 1N hydrochloric acid (×1). The 1N hydrochloric acid layer was adjusted to pH 9-10 with 1N aqueous sodium hydroxide solution and extracted with ethyl acetate (×1). The organic layer was dried over anhydrous sodium sulfate and concentrated. The residue was dissolved in methanol-4N hydrochloric acid/ethyl acetate (1.5 ml) and concentrated. The residue was crystallized from methanol/diethyl ether, and then the solid was collected by filtration and washed with diethyl ether, to give the title compound (90 mg, 67 %) as a colorless solid.
^{1}H NMR (400 MHz, DMSO-d_6) δppm; 3.46 (3H, s), 3.56 (6H, s), 6.51 (1H, d, J = 9.6 Hz), 7.33-7.39 (1H, m), 7.46-7.56 (4H, m), 8.14 (1H, d, J = 2.4 Hz), 8.31 (1H, s).
MS m/e (ESI) :365 (MH^+).

Comparative example 2 8-(3-Fluorophenyl)-2-iodo-9-(6-methoxy-3-pyridyl)-9H-6-purineamine

[0106]



(1) Synthesis of N1-(5-amino-4,6-dichloro-2-pyrimidinyl) acetamide

[0107] N1-(4,6-Dichloro-5-nitro-2-pyrimidinyl)acetamide (100 g, 0.40 mol) and Raney nickel (100 g, wet) were suspended in methanol (1.5 L) and stirred vigorously for 5 hours in a hydrogen atmosphere, at ordinary temperature and at normal pressure. After the nickel was filtered off, the filtrate was concentrated. The residue was crystallized from methanol/ethyl acetate, and the crystals were collected by filtration and washed with ethyl acetate, to give the title compound (44.6 g, 51 %) as a brown solid.
^{1}H-NMR(400MHz,DMSO-d_6) δppm 2.05(3H,s), 5.78(2H,s), 10.53(1H, s).

(2) N4-(6-Methoxy-3-pyridyl)-6-chloro-2,4,5-pyrimidine triamine

[0108] 5-Amino-2-methoxypyridine (12.4 g, 99.9 mmol) and conc. hydrochloric acid (3.0 ml) were added successively to a suspension of the compound (10.0 g, 45.2 mmol) obtained in (1) in water (200 ml) /ethanol (30 ml), and the mixture was heated under reflux for 3.5 hours. After cooling as it was, the reaction solution was neutralized with a saturated aqueous sodium bicarbonate solution, and the resulting crystals were collected by filtration, washed with water and air-dried at 50°C, to give the title compound (9.25g, 66%) as a reddish brown solid.
^{1}H NMR (400 MHz, DMSO-d_6) δppm; 3.83 (3H, s), 4.16 (2H, br s), 5.89(2H, br s), 6.78(1H, d, J=9.0Hz), 8.00 (1H, dd, J=2.6,9.0Hz), 8.36 (1H, s), 8.56 (1H, d, J = 2.6 Hz).

(3) 6-Chloro-8-(3-fluorophenyl)-9-(6-methoxy-3-pyridyl)-9H-2-purineamine

[0109] 3-Fluorobenzaldehyde (3.0 g, 24.2 mmol) and acetic acid (1.8 ml) were added successively to a suspension of the compound (6.0 g, 19.4 mmol) obtained in (2) in methanol (60 ml), and the mixture was stirred at room temperature for 15 hours. The reaction solution was concentrated and then subjected twice to azeotropic distillation with toluene. The resulting azeotropically distillated residue was suspended in ethanol (60 ml), and a solution of anhydrous iron (III) chloride in ethanol (30 ml) was added thereto at room temperature and heated under reflux for 3.5 hours. After cooling as it was, the reaction solution was concentrated. The residue was suspended in a small amount of methanol, and the solid was collected by filtration and washed with ethanol, to give the title compound (5.2 g, 72%) as a brown solid.
^{1}H NMR (400MHz, DMSO-d_6) δppm 3.91 (3H, s), 7.00 (1H, d, J=8.8Hz), 7.09 (2H, br s), 7.27-7.35 (3H, m), 7.42-7.48 (1H, m), 7.83(1H,dd, J=2.6,8.8Hz), 8.30 (1H, d, J=2.6Hz).

(4) 6-Chloro-8-(3-fluorophenyl)-2-iodo-9-(6-methoxy-3-pyridyl)-9H-2-purine

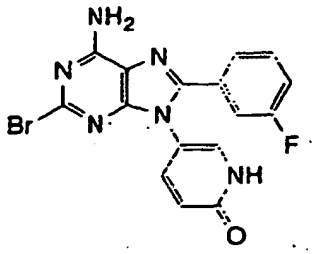
[0110] Copper (I) iodide (2.1 g, 11.0 mmol), diiodomethane (4.4 ml, 54.5 mmol) and isoamyl nitrite (4.4 ml, 32.8 mmol) were added successively to a solution of the compound obtained in (3) tetrahydrofuran (80 ml) at room temperature, and the mixture was stirred at 70 °C for 2 hours. After cooling as it was, the insoluble matters were filtered off. The filtrate was diluted with ethyl acetate and 1N hydrochloric acid, and the organic layer was washed with conc. ammonia water/saturated aqueous ammonium chloride solution (1 : 1) (×1) and a saturated aqueous ammonium chloride solution (×1), dried over anhydrous sodium sulfate and concentrated. The residue was suspended in diethyl ether, and the solid was collected by filtration and washed with diethyl ether, to give the title compound (2.98 g, 57 %) as a reddish brown solid.
^{1}H NMR (400MHz, DMSO-d_6) δppm 3.94 (3H, s), 7. 06 (1H, d, J=8.8Hz), 7.34-7.44 (3H, m), 7.48-7.55 (1H, m), 7.88 (1H, dd, J=2.8,8.8Hz), 8.34 (1H, d, J=2.8Hz).

(5) 8-(3-Fluorophenyl)-2-iodo-9-(6-methoxy-3-pyridyl)-9H-6-purineamine

[0111] A suspension of the compound (2.98 g, 61.9 mmol) obtained in (4) in 1,2-dimethoxyethane (60 ml)/conc. ammonia water (30 ml) was stirred for 6 hours in an autoclave at 70 °C. After cooling as it was, the reaction solution was concentrated. The residue was suspended in methanol, and the solid was collected by filtration and washed with methanol, to give the title compound (2.69 g, 94 %) as a colorless solid.
^{1}H NMR (400MHz, DMSO-d_6) δ ppm 3.92 (3H, s), 7.00 (1H, d, J=9.0Hz), 7.24-7.35 (3H, m), 7.42-7.49 (1H, m), 7.81 (1H, dd, J=2.6,9.0Hz), 7.92 (2H, br s), 8.25 (1H, d, J = 2.6 Hz).

Example 6 5-[6-Amino-2-bromo-8-(3-fluorophenyl)-9H-9-purinyl]-1,2-dihydro-2-pyridinone

[0112]

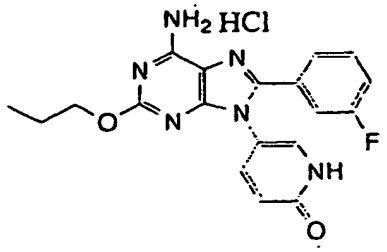


[0113] A suspension of the compound (100 mg, 0.216 mmol) in comparative Example 2 in a conc. aqueous hydrobromic acid solution (2 ml) was stirred at 100 °C for 15 minutes. After cooling as it was, the reaction solution was diluted with water, and the solid was collected by filtration and washed with water and ether, to give the title compound (71 mg, 79 %) as a colorless solid.

^{1}H NMR(400MHz,DMSO-d_6) δ ppm 6.45(1H,d,J=9.6Hz), 7.30-7.38(1H,m), 7.38-7.46(2H,m), 7.46-7.66(2H,m), 7.73 (1H,d,J=2.8Hz), 8.01(2H,br s).

Example 7 5-[6-Amino-8--(3-fluorophenyl)-2-propoxy-9H-9-purinyl]-1,2-dihydro-2-pyridinone hydrochloride

[0114]

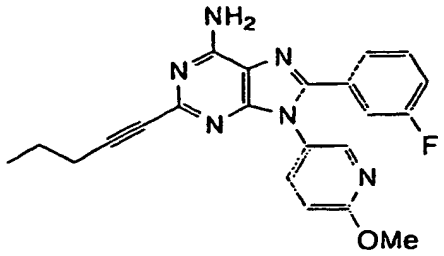


[0115] The compound (82 mg, 0.204 mmol) in Example 6 was added to a solution of sodium (30 mg, 1.30 mmol) in 1-propanol (3 ml) and heated under reflux for 4 hours. After cooling as it was, the reaction solution was diluted with a saturated aqueous ammonium chloride solution and ethyl acetate. The organic layer was washed with a saturated aqueous ammonium chloride solution (×1), dried over anhydrous sodium sulfate and concentrated. The residue was dissolved in methanol-5N hydrochloric acid (3 drops) and concentrated. The residue was crystallized from methanol/ether, and the solid was collected by filtration and washed with ether, to give the title compound (71 mg, 67 %) as a colorless solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm; 6.45 (1H, d, J = 9.6 Hz), 7.30-7.38 (1H,m), 7.38-7.46(2H,m), 7.46-7.66(2H,m), 7.73(1H,d,J=2.8Hz), 8.01(2H, br s).
MS m/e (ESI):381 (MH^+).

Comparative Example 3: 8-(3-Fluorophenyl)-9-(6-methoxy-3-pyridyl)-2-(1-pentynyl)-9H-6-purineamine

[0116]



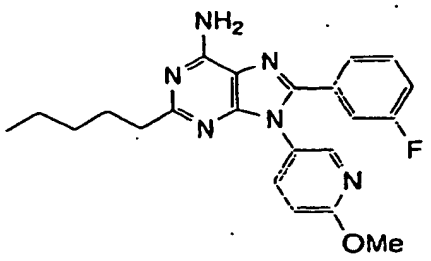
[0117] Triethylamine (0.2 ml, 1.43 mmol) was added dropwise to a suspension of the compound (200 mg, 0.433 mmol) in Comparative Example 2, copper (I) iodide (8 mg, 42.0 µmol), dichlorobis(triphenylphosphine) palladium (II) (30 mg, 42.7 µmol) and 1-pentyne (60 mg, 0.880 mmol) in N,N-dimethylformamide (3 ml) in a nitrogen atmosphere at room temperature, and the mixture was stirred for 18 hours. The reaction solution was diluted with a saturated aqueous ammonium chloride solution and ethyl acetate. The organic layer was washed with conc. ammonia water/saturated aqueous ammonium chloride solution (1:1) (×1) and a saturated aqueous ammonium chloride solution (×1), dried over anhydrous sodium sulfate and concentrated. The residue was suspended in diethyl ether, and the solid was collected by filtration and washed with diethyl ether, to give the title compound (148 mg, 85 %) as a pale brown solid.

^{1}H NMR (400MHz, DMSO-d_6) δppm 0.97(3H, t, J = 7.2 Hz), 1.53 (2H, sex, J = 7.2 Hz), 2.35 (2H, t, J = 7.2 Hz), 3.92

(3H, s), 7.01 (1H, d, J = 8.8 Hz), 7.26-7.38 (3H, m), 7.42-7.49 (1H, m), 7.61 (2H,br s), 7.80(1H, dd, J=2.8,8.8Hz), 8.24 (1H, d, J=2.8Hz).

Comparative Example 4 8-(3-Fluorophenyl)-9-(6-methoxy-3-pyridyl)-2-pentyl-9H-6-purineamine

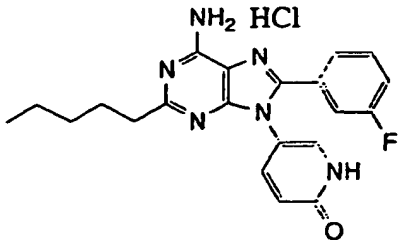
[0118]



[0119] After 10 % hydrous palladium-carbon (25 mg) was added to a solution of the compound (127 mg, 0.316 mmol) in Comparative Example 3 in methanol (20 ml) and stirred vigorously for 4.5 hours in a hydrogen atmosphere, at ordinary temperature and at normal pressure. After the palladium-carbon was filtered off, the filtrate was concentrated, to give the title compound (122 mg, 95 %) as a brown solid.
^{1}H NMR (400MHz, $CDCl_3$) δppm 0.88 (3H, t, J = 7.2 Hz), 1.27-1.40 (4H, m), 1.70-1.83 (2H, m), 2.75 (2H, t, J = 7.6 Hz), 3.98 (3H,s), 5.87(2H,br s), 6.85(1H,d,J=8.8Hz), 7.06-7.12(1H,m), 7.19-7.34 (3H,m), 7.53(1H, dd, J=2.8,8.8Hz), 8.13 (1H, d, J=2.8Hz).

Example 8 5-[6-Amino-8-(3-fluorophenyl)-9-(6-methoxy-3-pyridyl)-2-pentyl-9H-9-purinyl]-1,2-dihydro-2-pyridinone hydrochloride

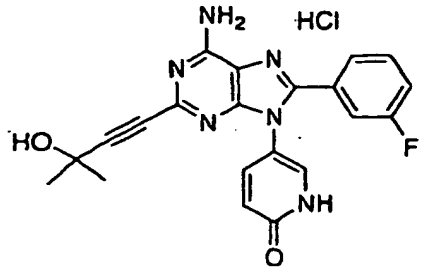
[0120]



[0121] 8-(3-Fluorophenyl)-9-(6-methoxy-3-pyridyl)-2-pentyl-9H-6-purineamine obtained in Comparative Example 4 was treated in the same manner as in Example 1 and converted into the hydrochloride, to give the title compound.
^{1}H NMR (400MHz, DMSO-d_6) δppm 0.86 (3H, t, J = 7.2 Hz), 1.25-1.37 (4H,m), 1.65-1.77(2H,m), 2.80(2H,t,J=7.6Hz), 6.47(1H,d,J=9.6Hz), 7.36-7.37(3H,m), 7.51(1H,dd,J=2.8,9.6Hz), 7.53-7.60(1H,m), 7.76(1H,d,J=2.8Hz).
MS m/e (ESI) : 393 (MH^+).

Example 9: 5-[6-Amino-8-(3-fluorophenyl)-2-(3-hydroxy-3-methyl-1-butynyl)-9H-9-purinyl]-1,2-dihydro-2-pyridinone hydrochloride

[0122]



1) 2-(Allyloxy)-5-nitropyridine

[0123] 60 to 70 % sodium hydride (3.0 g, 75.0 mmol) was added to a solution of allyl alcohol (8.6 g, 148 mmol) in N,N-dimethylformamide (100 ml) under ice-cooling in a nitrogen atmosphere and stirred. After foaming was confirmed to disappear, 2-bromo-5-nitropyridine (10.3 g., 50.7 mmol) was added thereto and stirred as such for 20 minutes. The reaction solution was diluted with a saturated aqueous ammonium chloride solution and extracted with ethyl acetate (×1). The organic layer was washed with a saturated aqueous ammonium chloride solution (×3), dried over anhydrous sodium sulfate and concentrated, to give the title compound 24 in crude form (9.9 g, quant.) as a dark brown solid.
^{1}H NMR (400MHz, DMSO-d_6) δ ppm 4.96 (2H, dt, J = 1.6, 5.6 Hz), 5.29 (1H, dq, J = 1.6, 10.4 Hz), 5.41 (1H, dq, J = 1.6, 17.2 Hz), 6.03-6.14(1H,m), 7.08(1H,d,J=9.2Hz), 8.50(1H,dd,J=2.8,9.2Hz), 9.08(1H,d,J=2.8Hz).

2) 6-(Allyloxy)-3-pyridineamine

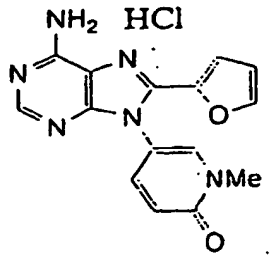
[0124] Zinc powder (20 g, 306 mmol) was added little by little to a suspension of the crude compound (9.9 g, 50.7 mmol) in 1) in ethanol (200 ml)/water (100 ml)/acetic acid (10 ml), and stirred for 30 minutes. After the insoluble matters were filtered off, the filtrate was diluted with ethyl acetate and a saturated aqueous ammonium chloride solution. The organic layer was washed with a saturated aqueous ammonium chloride solution (×1), 1 N aqueous sodium hydroxide (×1) and a saturated aqueous ammonium chloride solution (×1), dried over anhydrous sodium sulfate and concentrated, to give the title compound 25 in crude form (6.7 g, 88 %) as a black brown liquid. ^{1}H NMR (400 MHz, DMSO-d_6) δppm; 4.64 (2H, dt, J = 1.6, 5.2 Hz), 4.75 (2H, br s), 5.18 (1H, dq, J = 1.6, 10.4 Hz), 5.32 (1H, dq, J = 1.6, 17.2 Hz), 5.97-6.08 (1H, m), 6.57 (1H, d, J = 8.8 Hz), 7.01 (1H, dd, J = 2.8, 8.8 Hz), 7.48 (1H, d, J = 2.8 Hz).

3) 5-[6-Amino-8-(3-fluorophenyl)-2-(3-hydroxy-3-methyl-1-butynyl)-9H-9-purinyl]-1,2-dihydro-2-pyridinone hydrochloride

[0125] 10 % hydrous palladium-carbon (10 mg) and p-toluenesulfonic acid monohydrate (12 mg, 0.063 mmol) were added to a solution of the compound (90 mg, 0.202 mmol) in ethanol (10 ml) -water (2 ml), and the mixture was heated under reflux. After 30 minutes, p-toluenesulfonic acid monohydrate (110 mg, 0.578 mmol) was added thereto, and 1.5 hours thereafter, 10 % hydrous palladium-carbon (10 mg) and p-toluenesulfonic acid monohydrate (100 mg, 0.526 mmol) were additionally added thereto, and the mixture was heated under reflux for 3 days. After the palladium-carbon was filtered off, the filtrate was diluted with ethyl acetate and washed with a saturated aqueous ammonium chloride solution (×1). After extraction with 1N aqueous sodium hydroxide (×1), the aqueous layer was neutralized with 5N hydrochloric acid. The aqueous layer was extracted with ethyl acetate (×1), then dried over anhydrous sodium sulfate and concentrated. The residue was dissolved in methanol-5N hydrochloric acid (3 drops) and concentrated. The residue was crystallized from methanol/ethyl acetate/diethyl ether, and the solid was collected by filtration and washed with diethyl ether, to give the title compound 27 (18 mg, 20 %) as a pale yellow solid.
^{1}H NMR (400MHz, DMSO-d_6) δ ppm 1.45 (6H, s), 6.46 (1H, d, J=9.6Hz), 7.31-7.38 (1H, m), 7.40-7.47 (2H, m), 7.47-7.56 (2H,m), 7.73 (1H, d, J = 2.8 Hz).
MS m/e (ESI): 405 (MH^+).

Examples 10 5-[6-Amino-8-(2-furyl)-9H-9-purinyl]-1-methyl-1,2-dihydro-2-pyridinone hydrochloride

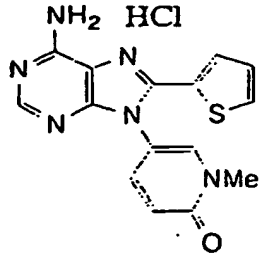
[0126]



[0127] Sodium methoxide (150 mg, 2.78mmol) was added to a methanol (8 ml) suspension of 5-[6-amino-8-(2-furyl)-9H-9-purinyl]-1,2-dihydro-2-pyridinone (400 mg, 1.36 mmol) synthesized in the same method as in Comparative Example 1 (2), (3) and (4) and Example 1, and the mixture was stirred in a nitrogen atmosphere at room temperature. After 15 minutes, iodomethane (0.26 ml, 4.18 mmol) was added thereto and further stirred for 16.5 hours. The reaction solution was concentrated, and the residue was subjected to silica gel column chromatography (eluting solvent: hexane, hexane/ethyl acetate=40:1, 20:1, 10:1). The crude product was suspended in ethanol, and the solid was collected by filtration and washed with ethanol and diethyl ether, to give the title compound in free form (337 mg). The resulting free compound was dissolved in methanol-4N hydrochloric acid/ethyl acetate (0.4 ml) and concentrated. The residue was crystallized from methanol/ethyl acetate/diethyl ether, and the solid was collected by filtration and washed with diethyl ether, to give the title compound (270 mg, 58 %) as a pale brown solid.
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm; 3.50 (3H, s), 6.58 (1H, d, J = 9.8 Hz), 6.68 (1H, dd, J = 1.6, 3.6 Hz), 6.74 (1H, d, J = 3.6 Hz), 7.60 (1H, dd, J = 3.2, 9.8 Hz), 7.96 (1H, d, J = 1.6 Hz), 8.24 (1H, d, J = 3.2 Hz), 8.41 (1H, s)
MS m/e (ESI) 309 (MH^+).

Example 11 5-[6-Amino-8-(2-thienyl)-9H-9-purinyl]-1-methyl 1,2-dihydro-2-pyridinone hydrochloride

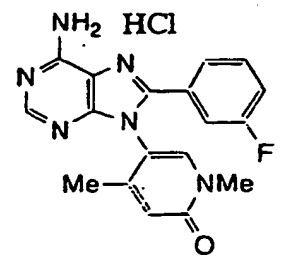
[0128]



[0129] The title compound was synthesized in the same manner as in Comparative Example 1 (2), (3) and (4), and Examples 1 and 10. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm; 3.51 (3H, s), 6.61 (1H, d, J = 9.6 Hz), 7.19 (1H, dd, J = 3.8, 5.0 Hz), 7.41 (1H, dd, J = 1.4, 3.8 Hz), 7. 62 (1H, dd, J = 2.8, 9.6 Hz), 7.83 (1H, dd, J = 1.4, 5.0 Hz), 8.30 (1H, d, J = 2.8 Hz), 8.45 (1H, s)
MS m/e (ESI) 325 (MH^+).

Example 12 5-[6-Amino-8-(3-fluorophenyl)-9H-9-purinyl]-1,4-dimethyl-1,2-dihydro-2-pyridinone hydrochloride

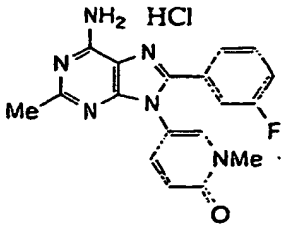
[0130]



[0131] The title compound was synthesized in the same manner as in Comparatire Example 1, and examples 1 and 10.
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm; 3.42 (3H, s), 6.46 (1H, s), 7.38-7.60 (4H, m), 8.13 (1H, s), 8.42 (1H, s)
MS m/e (ESI) 351 (MH^+).

Example 13 5-[6-Amino-8-(3-fluorophenyl)-2-methyl-9H-9-purinyl]-1-methyl-1,2-dihydro-2-pyridinone hydrochloride

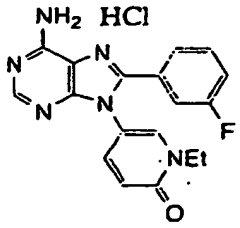
[0132]



[0133] The title compound was synthesized in the same manner as in Comparatire Example 1, and examples 1 and 10.
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm; 2.54 (3H, s), 3.43 (3H, s), 6.51 (1H, d, J = 10.0 Hz), 7.35-7.41 (1H, m), 7.44-7.57 (4H, m), 8.11 (1H, d, J = 2.8 Hz)
MS m/e (ESI) 351 (MH^+).

Example 14 5-[6-Amino-8-(3-fluorophenyl)-9H-9-purinyl]-1-ethyl-1,2-dihydro-2-pyridinone hydrochloride

[0134]

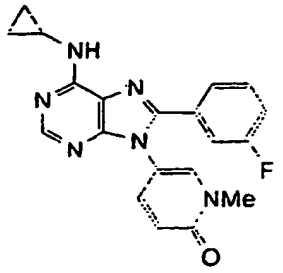


[0135] The title compound was synthesized in the same manner as in Example 10.
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm; 1.15 (3H, t, J = 7.2 Hz), 3.89 (2H, q, J = 7.2 Hz), 6.53 (1H, d, J = 9.6 Hz), 7.38-7.43 (1H, m), 7.45-7.49 (2H, m), 7.53 (1H, dd, J = 2.8, 9. 6 Hz), 7.54-7.60 (1H, m), 8.10 (1H, d, J = 2.8 Hz), 8.49 (1H, s)

MS m/e (ESI) 351 (MH^+).

Example 15 5-[6-(Cyclopropylamino)-8-(3-fluorophenyl)-9H-9-purinyl]-1-methyl-1,2-dihydro-2-pyridinone

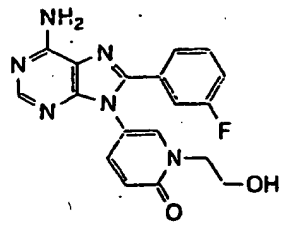
[0136]



[0137] The title compound was synthesized in the same manner as in Comparative Examples 1 (4), and examples 1 and 10.
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm; 0.62-0.67 (2H, m), 0.72-0.80 (2H, m), 2.94-3.20 (1H, br), 3.43 (3H, s), 6.46 (1H, d, J = 9.6 Hz), 7.28-7.34 (1H, m), 7.41-7.53 (4H, m), 8.09 (1H, d, J = 2.8 Hz), 8.11-8.28 (1H, br), 8.24 (1H, br s)
MS m/e (ESI) 377 (MH^+).

Example 16 5-[6-Amino-8-(3-fluorophenyl)-9H-9-purinyl]-1-(2-hydroxyethyl)-1,2-dihydro-2-pyridinone

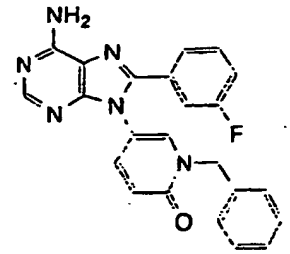
[0138]



[0139] The title compound was synthesized in the same manner as in Example 10.
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm; 3.58 (2H, q, J = 5.2 Hz), 3.93 (2H, t, J = 5.2 Hz), 4.86 (1H, t, J = 5.2 Hz), 6.49 (1H, d, J = 9.6 Hz), 7.29-7.36 (1H, m), 7.42-7.54 (6H, m), 7.94 (1H, d, J = 2.8 Hz), 8.15 (1H, s)
MS m/e (ESI) 367 (MH^+).

Example 17 5-[6-Amino-8-(3-fluorophenyl)-9H-9-purinyl]-1-benzyl-1,2-dihydro-2-pyridinone

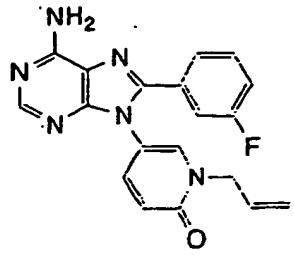
[0140]



[0141] The title compound was synthesized in the same manner as in Example 21.
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm; 5.04 (2H, s), 6.57 (1H, d, J = 9.6 Hz), 7.06-7.13 (2H, m), 7.26-7.44 (6H, m), 7.45-7.53 (3H, m), 7.63 (1H, dd, J = 3.2, 9.6 Hz), 8.13 (1H, d, J = 3.2 Hz), 8.16 (1H, s)
MS m/e (ESI) 413 (MH^+).

Example 18 1-Allyl-5-[6-amino-8-(3-fluorophenyl)-9H-9-purinyl]-1,2-dihydro-2-pyridinone

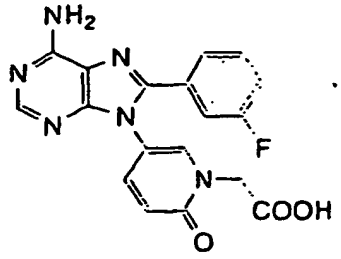
[0142]



[0143] The title compound was synthesized in the same manner as in Example 10.
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm; 4.49 (2H, d, J = 5.2 Hz), 4.90 (1H, d, J = 16.8 Hz), 5.10 (1H, d, J = 10.4 Hz), 5.88 (1H, ddd, J = 5.2, 10.4, 16.8 Hz), 6.54 (1H, d, J = 9.6 Hz), 7.30-7.35 (1H, m), 7.41-7.53 (5H, m), 7.45-7.53 (3H, m), 7.56 (1H, dd, J = 3.2, 9.6 Hz), 7.93 (1H, d, J = 3.2 Hz), 8.16 (1H, s)
MS m/e (ESI) 363 (MH^+).

Example 19 2-[5-[6-Amino-8-(2-furyl)-9H-9-purinyl]-2-oxo-1,2-dihydro-2-pyridinyl] acetic acid

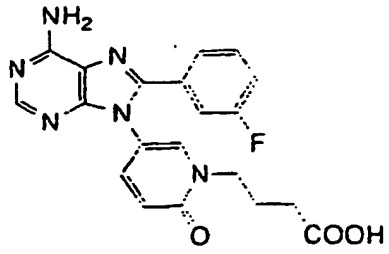
[0144]



[0145] 5N aqueous sodium hydroxide (2.0 ml, 10 mmol) was added to a solution, in methanol (6 ml)/tetrahydrofuran (6 ml) /water (10 ml), of ethyl 2-[5-[6-amino-8-(2-furyl)-9H-9-purinyl]-2-oxo-1,2-dihydro-2-pyridinyl] acetate (600 mg, 1.47 mmol) synthesized in the same manner as in Example 10, and the mixture was stirred at room temperature for 3 hours. The reaction solution was concentrated, dissolved in water and neutralized with 5N hydrochloric acid. The resulting crystals were collected by filtration and washed with water, to give the title compound (252 mg, 57 %) as a colorless solid.
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm; 4.61 (2H, s), 6.53 (1H, d, J = 9.6 Hz), 7.29-7.35 (1H, m), 7.45-7.52 (5H, m), 7.55 (1H, dd, J = 2.8, 9.6 Hz), 8.05 (1H, d, J = 2.8 Hz), 8.16 (1H, s)
MS m/e (ESI) 381 (MH^+).

Example 20 2-[5-[6-Amino-8-(2-furyl)-9H-9-purinyl]-2-oxo-1 2-dihydro-2-pyridinyl]butyric acid

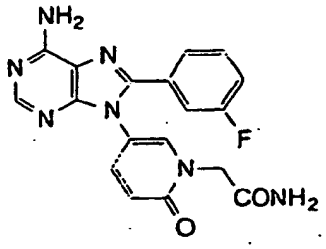
[0146]



[0147] The title compound was synthesized in the same manner as in Examples 10 and 19.
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm; 1.78 (2H, quint, J = 7.2 Hz), 2.12 (2H, t, J = 7.2 Hz), 3.89 (2H, t, J = 7.2 Hz), 6.51 (1H, d, J = 9.6 Hz), 7.28-7.34 (1H, m), 7.41-7.54 (6H, m), 7. 99 (1H, d, J = 2.8 Hz), 8.16 (1H, s)
MS m/e (ESI) 409 (MH^+).

Example 21 2-[5-[6-Amino-8-(2-furyl)-9H-9-purinyl]-2-oxo-1,2-dihydro-2-pyridinyl] acetamide

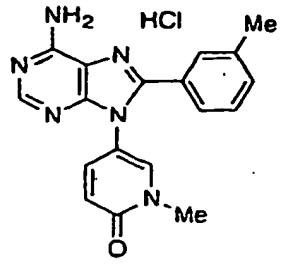
[0148]



[0149] A suspension of 2-[5-[6-amino-8-(2-furyl)-9H-9-purinyl]-2-oxo-1,2-dihydro-2-pyridinyl]acetic acid (150 mg, 0.394 mmol), 1-hydroxybenzotriazole (180 mg, 1.18 mmol), ammonium chloride (105 mg, 1.96 mmol), 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide (184 mg, 1.19 mmol) and triethylamine (0.28 ml, 2.00 mmol) in N,N-dimethylformamide (3 ml) was stirred at room temperature for 20 hours. The reaction solution was concentrated, and the residue was subjected to silica gel column chromatography (eluting solvent: dichloromethane, dichloromethane/methanol=20:1, 10:1, 4:1). The crude product was suspended in ethanol, and the solid was collected by filtration and washed with ethanol, to give the title compound (96 mg, 64 %) as a colorless solid.
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm; 4.51 (2H, s), 6.48 (1H, d, J = 9.6 Hz), 7.21 (1H, br s), 7.28-7.34 (1H, m), 7.45-7.54 (6H, m), 7.62 (1H, br s), 7.98 (1H, d, J = 2.8 Hz), 8.16 (1H, s) MS m/e (ESI) 380 (MH^+).

Example 22 5-[6-Amino-8-(3-methylphenyl)-9H-9-purinyl)-1-methyl-1,2-dihydro-2-pyridinone hydrochloride

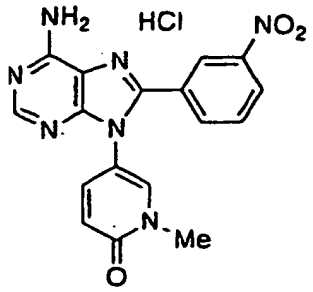
[0150]



[0151] The title compound was synthesized in the same manner as in Comparative Example 1 (2), (3) and (4) and Examples 1 and 4.
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm; 2.34 (3H, s), 3.45 (3H, s), 6.49 (1H, d, J = 9.2 Hz), 7.32-7.40 (3H, m), 7.47 (1H, dd, J = 9.2, 2.8 Hz), 7.61 (1H, s), 8.13 (1H, d, J = 2.8 Hz), 8.38 (1H, s) MS m/e (ESI) 333.01 (MH^+).

Example 23 5-[6-Amino-8-(3-nitrophenyl)-9H-9-purinyl]-1-methyl-1,2-dihydro-2-pyridinone hydrochloride

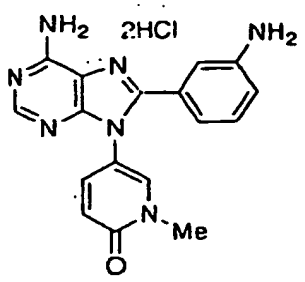
[0152]



[0153] The title compound was synthesized in the same manner as in Comparative Example 1 (2), (3) and (4), and Examples 1 and 4.
^{1}H NMR (400 MHz, DMSO-d_6) δppm; 3.44 (3H, s), 6.51 (1H, d, J=9.6Hz), 7.55 (1H, dd, J = 9.6, 3.0Hz), 7.79 (1H, t, J = 8.0 Hz), 8.00-8.04 (1H, m), 8.16 (1H, d, J = 3.0 Hz), 8.34 (1H, d, J = 2.4 Hz), 8.36 (1H, s), 8.62 (1H, t, J = 1.6 Hz) MS m/e (ESI) 364.00 (MH^+).

Example 24 5-[6-Amino-8-(3-aminophenyl)-9H-9-purinyl]-1-methyl-1,2-dihydro-2-pyridinone dihydrochloride

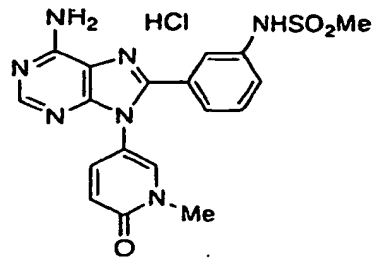
[0154]



[0155] The free amine (371 mg) obtained in Example 23 was dissolved in THF (200 ml) and EtOH (200 ml), and 10 % Pd-C (hydrous, 0.5 g) was added thereto, and the mixture was stirred for 2 hours in a hydrogen atmosphere at room temperature. The reaction mixture was filtered with Celite, and the filtrate was evaporated, to give 300 mg of the title compound in free form. This free amine (100 mg) was dissolved in methanol (2 ml), then 4N HCl/EtOAc (0.2 ml) was added thereto, and the precipitated crystals were collected by filtration, to give 84 mg of the title compound.
^{1}H NMR (400MHz, DMSO-d_6) δppm; 3.47 (3H, s), 6.50 (1H,d,J=9.6Hz), 7.21-7.27(1H,m), 7.33-7.38(1H,m), 7.42-7.53 (2H,m), 7.46(1H,dd,J=9.6,2.6Hz), 8.17(1H,d,J=2.6Hz), 8.49(1H,s) MS m/e (ESI)334.02 (MH^+).

Example 25 N-[3-[6-Amino-9-(1-methyl-6-oxo-1,6-dihydro-3-pyridinyl)-9H-8-purinyl]phenyl]methanesulfonamide hydrochloride

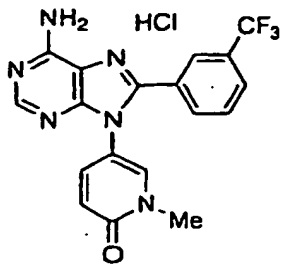
[0156]



[0157] The free amine (100 mg) obtained in Example 24 was dissolved in pyridine (2 ml), and methanesulfonyl chloride (28 µl) was added thereto under ice-cooling and stirred at 0 °C overnight. The reaction solution was evaporated and purified by silica gel column chromatography, to give 90 mg of the title compound in free form. This free amine was dissolved in methanol (2 ml), then 4 N HCl/EtOAc (0.6 ml) was added thereto, and the precipitated crystals were collected by filtration, to give 55 mg of the title compound.
^{1}H NMR (400 MHz, DMSO-d_6) δppm; 2.93 (3H, s), 3.46 (3H, s), 6.48 (1H, d, J = 9.6 Hz), 7.28-7.32 (1H, m), 7.42 (1H, dd, J = 9.6, 3.0 Hz), 7.46-7.50 (2H, m), 7.59 (1H, s), 8.18 (1H, d, J=3.0Hz), 8.45 (1H, s), 10.04 (1H, s)
MS m/e (ESI) 411.99 (MH^+).

Example 26 5-[6-Amino-8-(3-trifluoromethylphenyl)-9H-9-purinyl]-1-methyl-1,2-dihydro-2-pyridinone hydrochloride

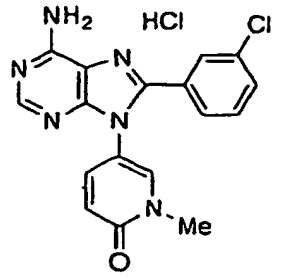
[0158]



[0159] The title compound was synthesized in the same manner as in Comparative Example 1 (2), (3) and (4), and Examples 1 and 4.
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm; 3.45 (3H, s), 6.53 (1H, d, J = 9.6 Hz), 7.54 (1H, dd, J = 9.6, 2.8 Hz), 7.75 (1H, t, J = 2.8 Hz), 7.88-7.93 (2H, m), 8.10 (1H, s), 8.17 (1H, d, J = 2.8 Hz), 8.43 (1H, s)
MS m/e (ESI) 387.00 (MH^+).

Example 27 5-[6-Amino-8-(3-chlorophenyl)-9H-9-purinyl]-1-methyl-1,2-dihydro-2-pyridinone hydrochloride

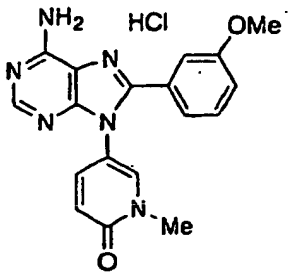
[0160]



[0161] The title compound was synthesized in the same manner as in Comparative Example 1 (2), (3) and (4), and Examples 1 and 4.
^{1}H-NMR(400MHz,DMSO-d_6) δ ppm; 3.43(3H,s), 6.50(1H,d,J=9.6Hz), 7.47-7.61(4H,m), 7.77-7.79(1H,m), 8.12(1H,d, J=2.8Hz), 8.34(1H,s)
MS m/e (ESI) 352.96 (MH^+).

Example 28 5-[6-Amino-8-(3-methoxyphenyl)-9H-9-purinyl]-1-methyl-1,2-dihydro-2-pyridinone hydrochloride

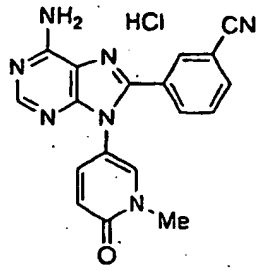
[0162]



[0163] The title compound was synthesized in the same manner as in Comparative Example 1 (2), (3) and (4), and Examples 1 and 4
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm; 3.43 (3H, s), 3.73 (3H, s), 6.50 (1H, d, J = 9.6 Hz), 7.06-7.11 (1H, m), 7.20-7.25 (2H, m), 7.38-7.43 (1H, m), 7.49 (1H, dd, J = 9.6. 2.8 Hz), 8.14 (1H, d, J = 2.8 Hz), 8.47 (1H, s)
MS m/e (ESI) 349.02 (MH^+).

Example 29 3-[6-Amino-9-(1-methyl-6-oxo-1,6-dihydro-3-pyridinyl)-9H-8-purinyl] benzonitrile hydrochloride

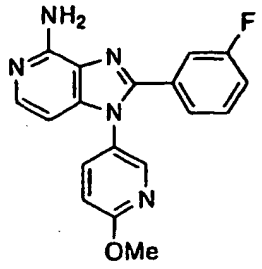
[0164]



[0165] The title compound was synthesized in the same manner as in Comparative Example 1 (2), (3) and (4), and Examples 1 and 4.
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm; 3.45 (3H, s), 6.51 (1H, d, J = 10.0 Hz), 7.50 (1H, dd, J = 10. 0, 2.8 Hz), 7.72 (1H, t, J = 8.0 Hz), 7.92-7.96 (1H, m)., 7.99-8.03 (1H, m),8.12-8.15 (1H,m), 8.14 (1H, d, J = 2.8 Hz), 8.42 (1H, s)
[0166] MS m/e (ESI) 343.99 (MH^+).

Comparative Example 5: 2-(3-Fluorophenyl)-1-(6-methoxy-3-pyridyl)-1H-imidazo[4,5-c]pyridine-4-amine

[0167]



(1) 2,4-Dichloro-3-nitropyridine

[0168] Phosphorus oxychloride (10 mL) was added to 2,4-dihydroxy-3-nitropyridine (2.5 g, 16 mmol) and stirred at 110°C for 4 hours. The reaction solution was evaporated. Ethyl acetate and iced water were added to the residue, which were then filtered through Celite. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, filtered through silica gel and concentrated, to give the title compound (2.7g, 87%) as a brown solid.

(2) N4-(6-Methoxy-3-pyridyl)-2-chloro-3-nitro-4-pyridineamine

[0169] A mixture of the compound (10.4 g, 54 mmol) obtained in (1), 5-amino-2-methoxypyridine (9.6 g, 77 mmol), trimethylamine (5.4 g, 54 mmol) and ethanol (40 mL) was stirred for 2 days at room temperature. The reaction solution was evaporated, and ethyl acetate and water were added to the residue. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated. The product was purified by silica gel column chromatography, to give the title compound (6.3g, 42%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm; 3.98 (3H, s), 6.63 (1H, d, J = 6.4 Hz), 6.85 (1H, d, J = 8.8 Hz), 7.46 (1H, dd, J = 8.8, 2.8 Hz), 7.92-7.96 (1H, m), 7.99 (1H, dd, J = 6.4, 0.8 Hz), 8.10 (1H, d, J = 2.8 Hz).

(3) N4-(6-Methoxy-6-pyridyl)-2-chloro-3,4-pyridinediamine

[0170] The compound (1.0 g) obtained in (2) was suspended in water (10 mL) and ethanol (20 ml), and zinc powder (1.0 g) and acetic acid (1 mL) were added thereto and stirred for 4 hours at room temperature. The reaction solution was filtered through Celite and evaporated. Ethyl acetate and a saturated aqueous sodium bicarbonate solution were added to the residue, which were then filtered. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, filtered with silica gel and concentrated, to give the title compound (0.85 g, 95 %). ^{1}H NMR (400MHz, $CDCl_3$) δ ppm; 3.95 (3H, s), 5.79 (1H, s), 6.59 (1H, d, J=5.6Hz), 6.79 (1H, d, J=8.8Hz), 7.42 (1H, dd, J=8.8,2.8Hz), 7.70 (1H, d, J=5.6Hz), 8.01 (1H, d, J=2.8Hz).

(4) N1-[2-Chloro-4-[(6-methoxy-3-pyridyl)amino)-3-pyridyl]-3-fluorobenzamide

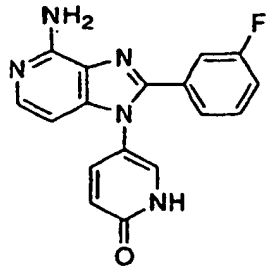
[0171] The compound (1.0 g, 4. 0 mmol) obtained in (3) was dissolved in pyridine (5 mL), and 3-fluorobenzoyl chloride (1.0 g) was added thereto under ice-cooling, and the mixture was stirred for 5 hours at room temperature. The reaction solution was evaporated, and the residue was diluted with ethyl acetate and washed with water and brine. The product was dried over anhydrous magnesium sulfate and concentrated. The product was purified by silica gel column chromatography, to give the title compound (1.2 g, 81 %).
^{1}H NMR (400MHz, $CDCl_3$) δ ppm; 3.95 (3H, s), 6.73 (1H, d, J=5.6Hz), 6.79 (1H, d, J = 8.4 Hz), 6.97 (1H, s), 7.31-7.37 (1H, m), 7.46 (1H, dd, J = 8.4, 2.8 Hz), 7.51 (1H, m), 7.69-7.79 (2H, m), 7.95 (1H, s), 7.96 (1H, d, J = 5.6 Hz), 8.07 (1H, d, J = 2.8 Hz).

(5) 4-Chloro-2-(3-fluorophenyl)-1-(6-methoxy-3-pyridyl)-1H-imidazo[4,5-c]pyridine

[0172] A mixture of the compound (980 mg, 2.6 mmol) obtained in (4), acetonitrile (20 mL) and phosphorus oxychloride (2 mL) was stirred at 80 °C for 3 hours. The reaction solution was evaporated, and the residue was diluted with ethyl acetate and washed with water and brine. The product was dried over anhydrous magnesium sulfate and concentrated. The product was purified by silica gel column chromatography, to give the title compound (680 mg, 73 %).
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm; 4.03 (3H, s), 6.91 (1H, dd, J=8.8,0.8Hz), 7.11 (1H, d, J=5.6 Hz), 7.11-7.17 (1H, m), 7.33-7.40 (3H, m), 7.47 (1H, dd, J=8.8,2.8Hz), 8.17 (1H, dd,

Example 30 5-[4-Amino-2-(3-fluorophenyl)-1H-imidazo[4,5-c]pyridin-1-yl]-1,2-dihydro-2-pyridinone

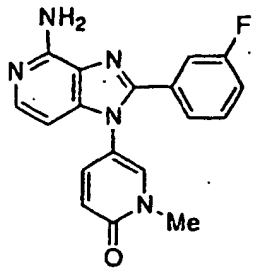
[0173]



[0174] A mixture of 2-(3-fluorophenyl)-1-(6-methoxy-3-pyridyl)-1H-imidazo[4,5-c]pyridine-4-amine (290 mL) obtained in Comparative Example 5 and conc. hydrochloric acid (10 mL) was stirred at 110°C for 7.5 hours. The reaction solution was evaporated, and the residue was purified by NH-form silica gel column chromatography, to give the title compound (120mg, 43%).
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm; 6. 39 (2H, br), 6.45 (1H, d, J = 9.6 Hz), 6.49 (1H, d, J = 5.8 Hz), 7.28-7.34 (1H, m), 7.40-7.54 (4H, m), 7.72 (1H, d, J = 5.8 Hz), 7.77 (1H, d, J = 2.8 Hz) MS m/e (ESI) 321.94 (MH^+).

Example 31 5-[4-Amino-2-(3-fluorophenyl)-1H-imidazo[4,5-clpyridin-1-yl]-1-methyl-1,2-dihydro-2-pyridinone

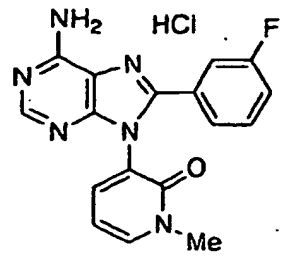
[0175]



[0176] 5-[4-Amino-2-(3-fluorophenyl)-1H-imidazo[4,5-c]pyridin-1-yl]-1,2-dihydro-2-pyridinone (100 mg) obtained in Example 30 was suspended in methanol (1 mL), and 28 % sodium methoxide-methanol solution (20 mL) and methyl iodide (20 mL) were added thereto and stirred.for 1 day at room temperature. The reaction solution was evaporated, and the residue was purified by NH-form silica gel column chromatography, to give the title compound (27 mg, 26 %).
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm; 3.45 (3H, s), 6.40 (2H, br), 6.49 (1H, d, J = 9.6 Hz), 6.56 (1H, d, J = 5.8 Hz), 7.29-7.34 (1H, m), 7.44-7.53 (4H, m), 7.73 (1H, d, J = 5.8 Hz), 8.17(1H,d,J=2.8 Hz)
MS m/e (ESI) 335.98 (MH^+).

Example 32 3-[6-Amino-8-(3-fluorophenyl)-9H-9-purinyl]-1-methyl-1,2-dihydro-2-pyridinone hydrochloride

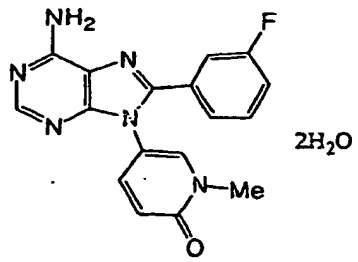
[0177]



[0178] The title compound was obtained in the same manner as in Comparative Examples 1, and examples 1 and 4.
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm; 3.46 (3H, s), 6.45 (1H, t, J = 7.0 Hz), 7.30-7.53 (4H, m), 7.91 (1H, dd, J = 7.2, 0.8 Hz), 7.97 (1H, dd, J = 7.2, 0.8 Hz), 8.33 (1H, s)
MS m/e (ESI) 336.97 (MH^+).

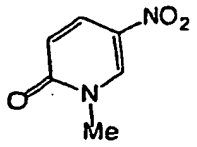
Example 33 5-[6-Amino-8-(3-fluorophenyl)-9H-9-purinyl]-1-methyl-1,2-dihydro-2-pyridinone

[0179]



(1) 1-Methyl-5-nitro-2 (1H)-pyridone

[0180]

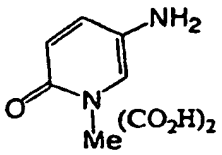


[0181] 5-Nitro-2-hydroxypyridine (0.55 kg, 3.93 mol), DMSO (2.2 L) and K_2CO_3 (0.88 kg, 6.37 mol) were introduced successively into a flask and stirred until foaming was terminated. Further, pTsOMe (0.88 kg, 4.71 mol) was added dropwise thereto in a warm bath at 37°C and stirred for 1 hour.

[0182] After 11 L water was added dropwise thereto, the reaction solution was ice-cooled, and the precipitated crystals were collected by filtration and dried in vacuo at 70°C, to give 516 g of the title compound (yield, 85 %) as a yellow powder.

(2) 5-Amimo-1-methyl-2 (1H)-pyridone oxalate

[0183]



[0184] 1-Methyl-5-nitro-2(1H)-pyridone (250 g, 1.62 mol), 10 % Pd-C (25 g, 0.1 w/w-%) and EtOH (2.5 L) were introduced into an autoclave and suspended. Hydrogen was introduced to keep 10 kg/cm^2, followed by leakage after 30 minutes, and the catalyst was separated off through Celite, and the resulting cake was further washed with EtOH (1.25 L).

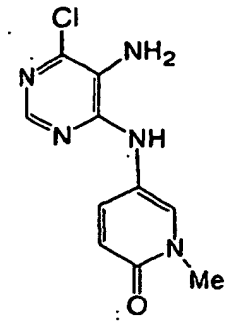
[0185] A solution of oxalic acid (293 g, 3.2 mol) in EtOH (2.5 L) was added dropwise to the filtrate and stirred in an ice-cold bath, and the resulting crystals were collected by filtration and washed with EtOH (1 L). The crystals were air-dried at 60°C, to give 182.6 g of the title compound (yield 52.6 %).

^{1}H NMR(DMSO-d_6) δppm 3.30(s,3H,N-Me), 6.25 (d, 1H, J=9.3Hz, H-3), 6.91(d,1H,J=2.9Hz,H-6), 7.07(dd,1H,J=9.3Hz, 2.9Hz,H-4)

m.p.: 224-226°C

(3) 5-(5-Amino-6-chloropyrimidine-4-yl)amino-1-methyl-1,2-dihydro-2-pyridinone

[0186]



[0187] 118.6 g of 5-amino-4,6-dichloropyrimidine, 170.0 g of 5-amino-1-methyl-2(1H)-pyridone oxalate, 360 mL EtOH and 2.4 L purified water were introduced successively to a flask and heated for 17 hours at a bath temperature of 110°C.

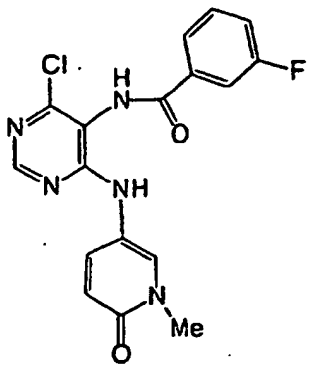
[0188] The reaction solution was cooled in an ice-cold bath, and 200 mL ammonia water was poured thereinto and stirred for 1 hour, and the crystals were collected by filtration, washed with 750 mL water and air-dried at 60°C, to give 188.2 g of the title compound as crude material.

[0189] Then, this crude material, 188 g, was suspended in 1.9 L (10 vol.) water, and 100 mL ammonia water was added thereto and stirred. After 2 hours, the crystals were collected by filtration, washed with 1 L water and air-dried at 60°C for 18 hours, to give 153.8 g of the title compound.

^{1}H NMR (DMSO-d_6) δ ppm; 3.42 (s, 3H, NMe-1'), 5.27 (brs, 2H, N2-5), 6.40 (d, 1H, J=9.7Hz, H-3'), 7.49 (dd, 1H, J=9.7Hz, 2.4Hz,H-4'), 7.77 (s, 1H, H-2), 7.98 (d, 1H, J=2.4Hz, H-6'), 8.35(s,1H,NH-4) m.p.: 258°C (decomp.)

(4) 5-[6-Chloro-5-(3-fluorobenzoyl)aminopyrimidin-4-yl]amino-1,2-dihydro-2-pyridinone

[0190]



[0191] 148.9 g 5-(5-amino-6-chloropyrimidine-4-yl)amino-1-methyl-1,2-dihydro-2-pyridinone and 1490 mL (10 vol.) pyridine were introduced into a flask and ice-cooled, and 98.1 mL (1.38 eq.) of 3-fluorobenzoyl chloride was added dropwise thereto.

[0192] After 1 hour, 1490 mL (10 vol) was poured into the reaction solution, evaporated, and 500 mL DME and 1490 mL water (10 vol) were poured successively into the residue and stirred at room temperature. The resulting crystals were collected by filtration, washed with 1600 mL DME/H_2O=1/5 and air-dried at 70°C for 24 hours, to give 196.4g of 5-[6-chloro-5-(3-fluorobenzoyl)aminopyrimidin-4-yl]amino-1,2-dihydro-2-pyridinone.

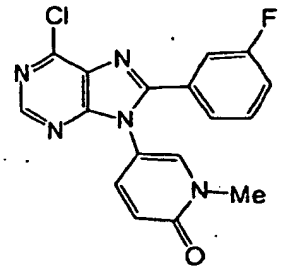
^{1}H NMR (DMSO-d_6) δ ppm; 3.41 (s, 3H, NMe-1'), 6.38 (d, 1H, J= 9.71 Hz, H-3'), 7.45-7.50 (m, 2H), 7.60 (dd, 1H, J= 14.0Hz, 7.0 Hz, H-5"), 7.78-7.90 (m, 3H), 8.30 (s, 1H, H-2), 9.09 (brs, 1H, NH-4), 10.08 (brs, 1H, NH-5)
m.p.: 173°C (decomp.)

(4-2) 5-[6-Chloro-5-(3-fluorobenzoyl)aminopyridine-4-yl]amino-1,2-dihydro-2-pyridinone hydrochloride

[0193] Acetonitrile (50 mL) was added to 5-[6-chloro-5-(3-fluorobenzoyl)aminopyrimidin-4-yl]amino-1,2-dihydro-2-pyridinone (2.0 g) and heated in an oil bath at 85 °C, and the insoluble matters were subjected to hot-filtration. The filtrate was diluted with acetonitrile (110 mL) and heated again to form a solution, and 4N HCl (1.30 mL, 0.97 eq.) was added thereto. Further, additional acetonitrile (20 mL) was added thereto and the crystals were collected by filtration, washed with acetonitrile (20 mL) and air-dried at 60°C, to give a pale bluish white powder (1.59 g, yield 72.5 %).
^{1}H NMR (DMSO-d_6) δ ppm 3.43 (s, 3H, NMe-1'),
6.43(d,1H,J=9.5Hz,H-3'), 7.40-7.53(m,2H), 7.60(dd,1H,J=14.0Hz, 8.0 Hz, H-5"), 7.77-7.93 (m, 3H), 8.31 (s, 1H, H-2), 9.16 (s, 1H, NH-4), 10.17 (s, 1H, NH-5)
m.p.: 193-195°C (decomp.)

(5) 5-[6-Chloro-8-(3-fluorophenyl)-9H-9-purinyl]-1-methyl-1,2-dihydro-2-pyridinone

[0194]



[0195] 186.0 g 5-[6-chloro-5-(3-fluorobenzoyl)aminopyridin-4-yl]amino-1,2-dihydro-2-pyridinone, 1.9 L CH_3CN, 186.0 mL $POCl_3$ (2.0 mol, 1 vol=4 eq.) were introduced into a flask and heated under reflux for about 6 hours in an oil bath (bath temperature, 120°C).

[0196] The reaction solution was concentrated, and 372 mL CH_3CN was added to and dissolved in it, and the solution was further evaporated. After it was concentrated, it was diluted with 1.9 L AcOEt, then 900 mL of 30 % aqueous K_2CO_3 solution was poured into it, and the mixture was partitioned by adding 1 L water and 1.9 L AcOEt. The organic layer was washed with 1.9 L water and evpoarated, to give 161.5 g (wet) 5-[6-chloro-8-(3-fluorophenyl)-9H-9-purinyl]-1-methyl-1,2-dihydro-2-pyridinone as a grayish green powder.
^{1}H NMR (DMSO-d_6) δ ppm 3.44(s, 3H,NMe-1'),
6.52(d,1H,J=9.7Hz,H-3'), 7.38-7.47 (m, 1H), 7.50-7.62 (m, 5H), 8.18 (d, 1H, J= 2.8 Hz, H-6'), 8.80 (d, 1H, J= 1.1 Hz, H-2)
m.p.: 219°C

(5-2) 5-[6-Chloro-8-(3-fluorophenyl)-9H-9-purinyl]-1-methyl-1,2-dihydro-2-pyridinone

[0197] 5-[6-Chloro-5-(3-fluorobenzoyl)aminopyrimidin-4-yl]amino-1,2-dihydro-2-pyridinone hydrochloride (5 g) and NMP (25 mL) were introduced into a flask and stirred at 110°C for 4 hours. The reaction solution was extracted with ethyl acetate (100 mL) and 10 % aqueous sodium bicarbonate solution (50 mL). After liquid partition, the organic layer was washed with brine (50 mL), and the organic layer in an amount of 1/5 of the original layer was used in the following crystallization.

[0198] After this organic layer was concentrated, DME (10 mL) was added to the concentrate which was then dissolved at 55 °C under stirring and crystallized by adding water (20 mL). The crystals were collected by filtration and dried at 50 °C for 16 hours, to give 0.64 g 5-[6-chloro-8-(3-fluorophenyl)-9H-9-purinyl]-1-methyl-1,2-dihydro-2-pyridinone as a slight brownish white compound (yield 73.8 %).

(5-3) 5-[6-Chloro-8-(3-fluorophenyl)-9H-9-purinyl]-1-methyl-1,2-dihydro-2-pyridinone

*HCl-EtOAc method

[0199] 5-[6-Chloro-5-(3-fluorobenzoyl)aminopyrimidin-4-yl]amino-1,2-dihydro-2-pyridinone (1 g, 2.7 mmol) was dissolved in NMP (10 mL), and 4N HCl/EtOAc (0.8 mL, 3.2 mmol) was added thereto and stirred under heating at 110 °C

for 14 hours. By analyzing the reaction solution in HPLC, it was confirmed that 5- [6-chloro-8-(3-fluorophenyl)-9H-9-purinyl]-1-methyl-1,2-dihydro-2-pyridinone (90.2 %) was formed.

(5-4) 5-[6-Chloro-8-(3-fluorophenyl)-9H-9-purinyl]-1-methyl-1,2-dihydro-2-pyridinone

*Non-catalytic method

[0200] 5-[6-Chloro-5-(3-fluorobenzoyl)aminopyrimidin-4-yl]amino-1,2-dihydro-2-pyridinone (1g, 2.7mmol) was dissolved in NMP (2mL) and stirred under heating at 140°C for 10 hours. By analyzing the reaction solution in HPLC, it was confirmed that 5-[6-chloro-8-(3-fluorophenyl)-9H-9-purinyl]-1-methyl-1,2-dihydro-2-pyridinone (91.3%) was formed.

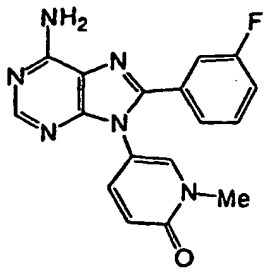
(5-4) 5-[6-Chloro-8-(3-fluorophenyl)-9H-9-purinyl]-methyl-1,2-dihydro-2-pyridinone

[0201] (One-pot reaction: 5-(5-amino-6-chloropyrimidin-4-yl)amino-1-methyl-1,2-dihydro-2-pyridinone→5-[6-chloro-5-(3-fluorobenzoyl)aminopyrimidin-4-yl]amino-1,2-dihydro-2-pyridinone→5-[6-chloro-8-(3-fluorophenyl)-9H-9-purinyl]-1-methyl-1,2-dihydro-2-pyridinone)

[0202] 5-(5-Amino-6-chloropyrimidin-4-yl)amino-1-methyl-1,2-dihydro-2-pyridinone (1 g) and NMP (10 mL) were introduced into a flask and stirred at 40 °C. 3-Fluorobenzoyl chloride (0.53 mL, 1.1 eq.) was added dropwise to this suspension, and after additional NMP (3.2 mL) was added thereto and stirred for about 1.5 hours, the reaction solution was elevated to 110 °C and stirred for 3 hours. Ethyl acetate (33 mL) and 10 % aqueous sodium bicarbonate solution (16.5 mL) were added to the reaction solution, and the organic layer was washed with brine (16.5 mL) and concentrated. The concentrate was dissolved by adding DME (16.5 mL) and stirring it at 55°C, and then crystallized by adding water (33 mL). The crystals were collected by filtration and dried at 50 °C for 4 hours, to give 0.94 g of 5-[6-chloro-8-(3-fluorophenyl)-9H-9-purinyl]-1-methyl-1,2-dihydro-2-pyridinone (two-steps, yield 66.7 %).

(6) 5-[6-Amino-8-(3-fluorophenyl)-9 H-9-purinyl]-1-methyl-1,2-dihydro-2-pyridinone

[0203]

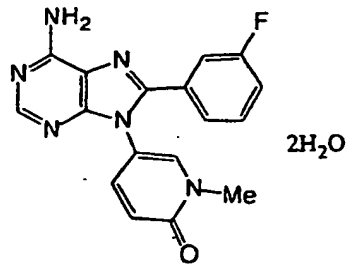


[0204] 160.0 g crude crystals (wet) of 5-[6-chloro-8-(3-fluorophenyl)-9H-9-purinyl]-1-methyl-1,2-dihydro-2-pyridinone (content 96.0 %; net weight, 155 g), 2600 mL DME and 1300 mL conc. ammonia water (28-30 %) were introduced into an autoclave and heated at an external temperature of 75°C. After 1.5 hours, the external temperature was elevated to 90°C, and the mixture was stirred for 8.5 hours in total after heating was initiated.

[0205] 6.5 L deionized water was added to the reaction solution which was then ice-cooled, and the precipitated crystals were collected by filtration, washed with 500 mL water and dried, to give 135.0 g of the title compound.

(7) 5-[6-Amino-8-(3-fluorophenyl)-9H-9-purinyl]-1-methyl-1,2-dihydro-2-pyridinone $2H_2O$

[0206]



[0207] 130 g crude crystals of 5-[6-amino-8-(3-fluorophenyl)-9H-9-purinyl]-1-methyl-1,2-dihydro-2-pyridinone, 1.3 L methanol-modified ethanol (mixture of EtOH/MeOH in a ratio of 2000 mL/50 g) and 1.3 L water were introduced into a flask and heated in a water bath at 90°C.

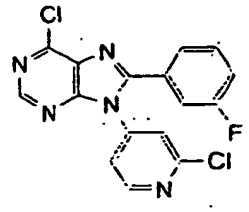
[0208] After the heater was turned off, the mixture was stirred at a decreasing temperature, and the precipitated crystals were collected by filtration and washed with 200 mL methanol-modified ethanol. The product was dried under reduced pressure, to give 119.1 g of the title compound.

^{1}H NMR (DMSO-d_6) δ ppm; 3.43 (s, 3H, NMe-1'), 6.46 (d, 1H, J=9.7Hz, H-3'), 7.26-7.36 (m, 1H), 7.36-7.60 (m, 6H), 8.09 (d, 1H, J=2.8Hz, H-6'), 8.14 (s, 1H, H-2)

m.p.: 244°C (decomp.)

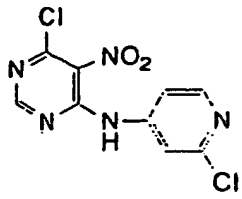
Comparative example 6: 6-Chloro-9-(2-chloro-4-pyridyl)-8-(3-fluorophenyl)-9H-purine

[0209]



(1) N-(6-Chloro-5-nitro-4-pyrimidinyl)-N-(2-chloro-4-pyridyl)amine

[0210]

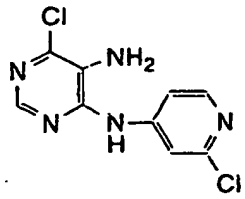


[0211] 4-Amino-2-chloropyridine (8.0 g, 62.2 mmol) and triethylamine (8.7 mL) were added successively to a suspension of 5-nitro-4,6-dichloropyrimidine (8.0 g, 41.2 mmol) in tetrahydrofuran (160 mL), and the mixture was heated under reflux for 4 hours. After cooling as it was, the reaction solution was diluted with ethyl acetate (160 ml) and washed with 160 ml water and brine, and the organic layer was dried over anhydrous magnesium sulfate. The solvent was evaporated, and the residue were suspended in diethyl ether, and the resulting solid was collected by filtration and air-dried, to give the title compound (2.2 g, 19 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm; 7.39 (1H, dd, J = 1.9, 5.5 Hz), 7.79 (1H, d, J = 2.0 Hz), 8.31 (1H, d, J = 5.6), 8.62 (1H, s), 9.14 (1H, bs)

(2) N4-(2-Chloro-4-pyridyl)-6-chloro-4,5-pyrimidine diamine

[0212]

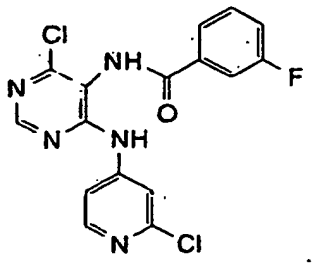


[0213] N-(6-Chloro-5-nitro-4-pyrimidinyl)-N-(2-chloro-4-pyridyl)amine (2.2 g, 7.6 mmol) was suspended in 44 ml ethanol and 4.4 ml acetic acid, and 2.2 g zinc powder was added little by little thereto at 0 °C. The reaction solution was returned to room temperature and stirred for 1 hour, and then the insoluble matters were filtered off. The filtrate was concentrated and suspended in water, and the resulting solid was collected by filtration and air-dried, to give 2.5 g of the title compound in crude form.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm; 7.52 (1H, dd, J = 2.0, 5.9), 7.84 (1H, J = 2.0), 8.12 (1H, J = 5.5), 8.13 (1H, s)

(3) N1-{4-Chloro-6-[(2-chloro-4-pyridyl)amino]-5-pyrimidinyl}-3-fluorobenzamide

[0214]



[0215] 3-Fluorobenzoyl chloride (1.3 mL, 10.7 mmol) was added dropwise to a suspension of N4-(2-chloro-4-pyridyl)-6-chloro-4,5-pyrimidine diamine (2.5 g, 9.8 mmol) in pyridine (50 mL) over 5 minutes in a nitrogen atmosphere at 0 to 5 °C, and the mixture was stirred as such for 12 hours. The reaction solution was diluted with water and ethyl acetate (100 mL) . The organic layer was washed with 1N hydrochloric acid (×1). After the 1N hydrochloric acid layer was extracted with ethyl acetate (×2), the combined organic layers were washed with a saturated aqueous sodium bicarbonate solution (×1), dried over anhydrous sodium sulfate and concentrated. The residue was suspended in diethyl ether, and the solid was collected by filtration and washed with diethyl ether, to give the title compound (2.3 g, 62 %) as a colorless solid.

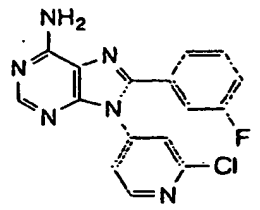
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm; 7.38-7.42 (2H, m), 7.56-7.62 (1H,m), 7.70-7.78(3H,m), 7.99(1H,bs), 8.27(1H,d, J=5.7), 8.60(1H,s)

[0216] Then, a suspension of N1-{4-chloro-6-[(2-chloro-4-pyridyl)amino]-5-pyrimidinyl}-3-fluorobenzamide (2.3 g, 6.1 mmol) in phosphorus oxychloride (75 mL) was heated under reflux for 1.5 hours in a nitrogen atmosphere. After cooling as it was, the reaction solution was evaporated. The residue was diluted with ethyl acetate (100 ml), washed with water (×3), a saturated aqueous sodium bicarbonate solution (×2) and brine (×1), dried over sodium sulfate anhydride and concentrated. The residue was suspended in diethyl ether, and the solid was collected by filtration and washed with diethyl ether, to give the title compound (1.0 g, 46 %) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm; 7.21 (1H, d, J = 1.8, 5.3 Hz), 7.24-7.30 (2H, m), 7.39-7.48 (3H, m), 8.56 (1H, d, J = 5.3 Hz), 8.79 (1H, s).

Comparative Example 7: 9-(2-Chloro-4-pyridyl)-8-(3-fluorophenyl)-9H-6-purineamine

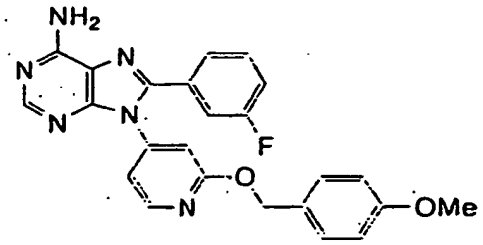
[0217]



[0218] A suspension of 6-chloro-9-(2-chloro-4-pyridyl)-8-(3-fluorophenyl)-9H-purine (325 mg, 0.9 mmol) in Comparative Example 6 in 1,2-dimethoxyethane (10 mL)/conc. ammonia water (5 mL) was stirred for 11 hours in an autoclave at 80 °C. After cooling as it was, the reaction solution was diluted with a saturated aqueous ammonium chloride solution and ethyl acetate. The organic layer was washed with a saturated aqueous ammonium chloride solution (×1), dried over anhydrous sodium sulfate and concentrated. The residue was suspended in diethyl ether, and the solid was collected by filtration and washed with diethyl ether, to give the title compound (229 mg, 75 %) as a colorless solid.
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm; 5.75 (2H, br), 7.16-7.24 (2H, m), 7.31-7.41 (2H, m),7.44 (1H, d, J = 1.8Hz), 8.41 (1H, s), 8.51 (1H, d, J = 5.3 Hz), 8.14 (1H, s), 8.23 (1H, d, J = 2.8 Hz).

Comparative Example 8: 8-(3-Fluorophenyl)-9-{2-[(4-methoxybenzyl)oxy]-4-pyridyl}-9H-6-purineamine

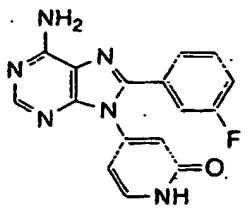
[0219]



[0220] 200 mg metal sodium was dissolved in 4-methoxybenzyl alcohol at 80 °C, and 9-(2-chloro-4-pyridyl)-8-(3-fluorophenyl)-9H-6-purineamine (596 mg, 1.75 mmol) in Comparative Example 7 was added thereto and stirred for 1 hour. After cooling as it was, the reaction solution was diluted with water and extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and evaporated. The residue was suspended in a mixture of ethyl acetate and hexane, and the formed solid was collected by filtration and washed with diethyl ether, to give the title compound (690 mg, 89 %) as a colorless solid.
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm; 3.80 (3H, s), 5.34 (2H, s), 6.13 (2H, bs), 6.80-6.88 (2H, m), 6.90 (2H, d, J = 8.1 Hz), 7.10-7.16 (1H, m), 7.23-7.35 (2H, m), 7.37 (2H, d, J = 8.2 Hz), 8.28 (1H, d, J = 5.3 Hz), 8.36 (1H, s).

Example 34 4- [6-Amino-8-(3-fluorophenyl)-9H-9-purinyl]-1,2-dihydro-2-pyridinone

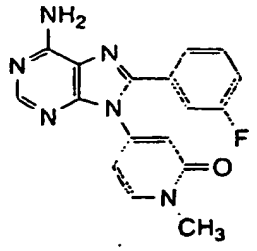
[0221]



[0222] 8-(3-Fluorophenyl)-9-{2-[(4-methoxybenzyl)oxy]-4-pyridyl}-9H-6-purineamine (690 mg, 1.56 mmol) in Comparative Example 8 was dissolved in 3.5 ml trifluoroacetic acid and reacted at room temperature for 30 minutes. The reaction solution was diluted with water and the resulting precepitates were collected by filtration, washed with water and dried, to give the title compound (510 mg, 75 %) as trifluoroacetate.
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm; 6.15 (1H, d, J = 5.1 Hz), 6.43 (1H, d, J= 1.8 Hz), 7.32-7.54 (5H, m), 8.22 (1H, s).

Example 35 4-[6-Amino-8-(3-fluorophenyl)-9H-9-purinyl]-1-methyl-1,2-dihydro-2-pyridinone

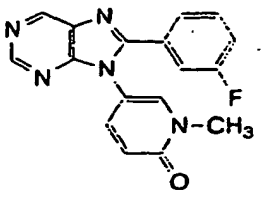
[0223]



[0224] 4-[6-Amino-8-(3-fluorophenyl)-9H-9-purinyl]-1,2-dihydro-2-pyridinone (50 mg, 0.16 mmol) in Example 34 was dissolved in 1 ml N,N-dimethylformamide, and 64 mg anhydrous potassium carbonate and 15 µl methyl iodide were added thereto and reacted at 60 °C for 2 hours. The reaction solution was cooled, then the insoluble matters were filtered off, and the filtrate was concentrated to dryness. The residue was purified by a silica gel column (eluted with ethyl acetate) and concentrated, to give the title compound (30 mg, 55 %).
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm; 3.53 (3H,s), 5.89 (2H, bs), 6.20 (1H, dd, J= 2.2, 7.1 Hz), 6.46 (1H, d, J = 2.3 Hz), 7.38 (1H, d, J= 7.1 Hz), 8.32 (1H, s).
MS m/e (FAB) 337 (MH^+).

Example 36 5-[8-3(Fluorophenyl)-9H-9-purinyl] 1-methyl-1,2-dihydro-2-pyridinone

[0225]



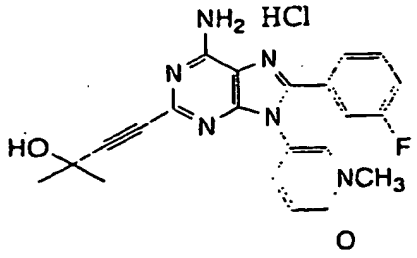
[0226] 5-[6-Amino-8-(3-fluorophenyl)-9H-9-purinyl]-1-methyl-1,2-dihydro-2-pyridinone (1.0 g, 3.0 mmol) in Example

33 was dissolved in 20 ml tetrahydrofuran, and 1.2 ml isoamyl nitrite was added thereto and heated for 2 hour under reflux. The reaction solution was cooled and evaporated, and the residue was purified by a silica gel column. The desired product was eluted with ethyl acetate and then the solvent was removed, to give the title compound (340 mg, 35 %).

^{1}H NMR (400MHz, $CDCl_3$) δ ppm 3.62 (3H, s), 6.68 (1H, d, J = 9.7), 7.21 (1H, dd, J = 2.9, 9.7), 7.23-7.27 (1H, m), 7.41-7.49 (2H,m), 7.53-7.57(1H, m), 7.58 (1H, d, J=2.8), 9.00 (1H,s), 9.23 (1H, s).
MS m/e (ESI) 322 (MH^+).

Example 37 5-[6-Amino-8-(3-fluorophenyl)-2-(3-hydroxy-3-methyl-1-butynyl)-9H-9-purinyl]-1-methyl-1,2-dihydro-2-pyridinone

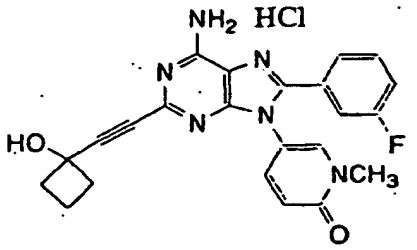
[0227]



[0228] The compound obtained in Example 9 was treated in the same manner as in Example 10, to give the title compound.
^{1}H NMR (400MHz, $CDCl_3$) δ ppm 1.63 (6H, s), 3.60 (3H, s), 6.20-6.40 (2H, br), 6.62 (2H, dd, J = 1.6, 9.3 Hz), 7.10-7.20 (2H, m), 7.30-7.44 (3H, m), 7.57 (1H, bs).
MS m/e (FAB) 419 (MH^+).

Example 38 5-{6-Amino-8-(3-fluorophenyl)-2-[2-(1-hydroxycyclobutyl)-1-ethynyl]-9H-9-purinyl}-1-methyl-1,2-dihydro-2-pyridinone hydrochloride

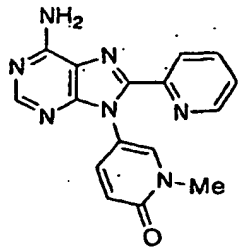
[0229]



[0230] The title compound was obtained by treatment in the same manner as in Example 10.
^{1}H NMR (400 MHz, $CDCl_3$) δppm; 1.75-1.83 (2H, m), 2.21-2.30 (2H,m), 2.50-2.60(2H,m), 3.54(3H,s), 6.10(2H,bs), 6.56(2H,d,J=9.7Hz), 7.07 (1H,dd, J=2.9,9.7Hz), 7.08-7.14 (1H, m), 7.26-7.38(3H,m), 7.50 (1H, d, J = 2.4Hz).
MS m/e (FAB) 431 (MH^+).

Example 39 5-[6-Amino-8-(2-pyridyl)-9H-9-purinyl]-1-methyl-1 2-dihydro-2-pyridinone

[0231]



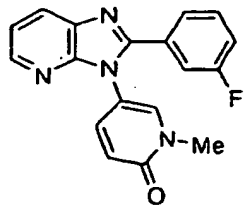
[0232] A solution of 150 mg of 5- [6-amino-8-(2-pyridyl) -9H-9-purinyl)-2-pyridinol, 133 mg of sodium methoxide and 306 µL methyl iodide in 20 mL mixture of methanol and tetrahydrofuran in a ratio of 1/1 was stirred at room temperature for 2 hours and 35 minutes and then at 60 °C for 45 minutes. Ethyl acetate and water were added to the reaction mixture, and this mixture was extracted once with ethyl acetate. The organic layer was washed with brine, and the whole aqueous layer was extracted twice with ethyl acetate. The whole organic layer was dried over magnesium sulfate and filtered, and from the resulting residues, the solvent was evaporated, to give 90 mg of the title compound as brown crystals (58 % y.).

^{1}H NMR (400MHz, DMSO-d_6) δppm; 3.44 (1H, s), 6.43 (1H, d, J=9.2Hz), 7.42-7.47 (2H, m), 7.53 (2H, brs), 7.96-8.02 (2H, m), 8.16-8.12 (2H,m), 8.49-8.50 (2H, m)

MS m/e (ESI) (MH^+).

Example 40 5-[2-(3-Fluorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl]-1-methyl-1,2-dihydro-2-pyridinone

[0233]



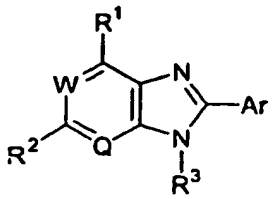
[0234] A solution of 250 mg of 5-[2-(3-fluorophenyl)-3H-imidazo[4,5-b]pyridin-3-yl]-2-pyridinol, 177 mg of sodium methoxide and 306 µL methyl iodide in a mixture (10 mL) of methanol and tetrahydrofuran in a ratio of 1/1 was stirred at room temperature for 1 day. Ethyl acetate and a saturated aqueous ammonium chloride solution were added thereto and the mixture was extracted 3 times with ethyl acetate. The organic layer was washed once with brine and dried over magnesium sulfate followed by distilling the solvent away under reduced pressure, to give crude crystals. The resulting crude crystals were collected by filtration with diethyl ether, to give 160 mg of the title compound as brown crystals (61% y.).

^{1}H NMR (400MHz, DMSO-d_6) δ ppm; 3.46 (1H, s), 6.51 (2H, d, J=9.6Hz), 7.38-7.44 (2H, m), 7.55-7.59 (4H, m), 8.18 (1H, s), 8.23(1H,d,J=8.0Hz), 8.39 (1H, d, J=4.8Hz)

MS m/e (ESI) (MH^+).

Claims

1. A condensed imidazole compound, a pharmacologically acceptable salt thereof or hydrates thereof, which is represented by the formula (I):



(I)

(wherein R^1 represents hydrogen, or formula $-NR^4R^5$ (wherein R^4 and R^5 are the same as or different from each other and each represents hydrogen, C3-C8 cycloalkyl group or a C1-C8 alkyl group); R^2 represents 1) hydrogen, 2) a halogen atom, 3) a C2-C8 alkynyl group, which may be substituted with a hydroxyl group or C3-C6 cycloalkyl group, 4) a C1-C8 alkyl group, or 5) a C1-C8 alkoxy group ; R^3 represents a 1,2-dihydro-2-oxopyridyl group which may be substituted with a) a halogen atom or a C1-C6 alkyl group, and whose nitrogen atom may further be substituted with b-1) a C1-C6 alkyl group which may be substituted with a halogen atom, hydroxyl, phenyl, C2-C8 alkynyl or an optionally protected carboxyl group, b-2) an optionally substituted C3-C6 cycloalkyl-C1-C4 alkyl group or b-3) an optionally substituted C3-C6 cycloalkyl group, Ar represents 1) an optionally substituted phenyl group, 2) an optionally substituted pyridyl group, 3) an optionally substituted furyl group, or 4) an optionally substituted thienyl group; and Q and W are both N or one of Q and W is N and the other is CH.

2. The condensed imidazole compound according to claim 1, a pharmacologically acceptable salt thereof or hydrates thereof, wherein R^2 is hydrogen atom.

3. The condensed imidazole compound according to claim 1 or 2, a pharmacologically acceptable salt thereof or hydrates thereof, wherein Ar is an optionally substituted phenyl.

4. The condensed imidazole compound according to any of claims 1 to 3, a pharmacologically acceptable salt thereof or hydrates thereof, wherein Ar is a phenyl substituted with a halogen atom.

5. The condensed imidazole compound according to any of claims 1 to 4, a pharmacologically acceptable salt thereof or hydrates thereof, wherein R^1 is represented by the formula - NR^4R^5 (wherein R^4 and R^5 are the same as or different from each other and each represents hydrogen or a C1-C8 alkyl group

6. The condensed imidazole compound according to any of claims 1 to 5, a pharmacologically acceptable salt thereof or hydrates thereof, wherein R^1 is amino.

7. The condensed imidazole compound according to any of claims 1 to 6, a pharmacologically acceptable salt thereof or hydrates thereof, wherein R^1 is amino and R^2 is hydrogen.

8. The condensed imidazole compound according to any of claims 1 to 7, a pharmacologically acceptable salt thereof or hydrates thereof, wherein R^1 is amino, R^2 is hydrogen, and R^3 is a 1,2-dihydro-2-oxopyridyl group whose nitrogen may be substituted with a C1 to C6 alkyl group which may be substituted with a halogen atom,

9. The condensed imidazole compound according to claim 1, which is 5-[6-amino-8-(3-fluorophenyl)-9 H-9-purinyl]-1-methyl-1, 2-dihydro-2-pyridinone, and a pharmacologically acceptable salt thereof or hydrates thereof.

10. The condensed imidazole compound according to claim 1, a pharmacologically acceptable salt thereof or hydrates thereof, which is a purine compound wherein each of Q and W means nitrogen.

11. The condensed imidazole compound according to claim 1, a pharmacologically acceptable salt thereof or hydrates thereof, which is an imidazopyridine compound wherein one of Q and W is N, and the other is -CH.

12. The condensed imidazole compound according to claim 1, a pharmacologically acceptable salt thereof or hydrates thereof, which is 5-{6-Amino-8-(3-fluorophenyl)-2-[2-(1-hydroxycyclobutyl)-1-ethynyl]-9H-9-purinyl}-1-methyl-1,2-dihydro-2-pyridinone.

13. A pharmaceutical composition comprising the condensed imidazole compound according to any of claims 1 to 12, a pharmacologically acceptable salt thereof or hydrates thereof and optionally a pharmacologically acceptable

carrier.

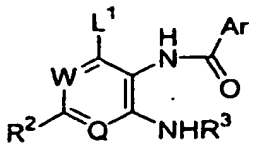
14. Use of the condensed imidazole compound according to any of claims 1 to 12, a pharmacologically acceptable salt thereof or hydrates thereof for preparing a medicament for preventing or treating diabetes mellitus.

15. Use of the condensed imidazole compound according to any of claims 1 to 12, a pharmacologically acceptable salt thereof or hydrates thereof for preparing a medicament for preventing or treating diabetic complications.

16. Use of condensed imidazole compound according to any of claims 1 to 12, a pharmacologically acceptable salt thereof or hydrates thereof for preparing a medicament for preventing or treating diabetic retinopathy.

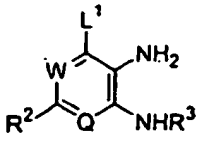
17. Use of the condensed imidazole compound according to any of claims 1 to 12, a pharmacologically acceptable salt thereof or hydrates thereof for preparing a medicament having adenosine A2 receptor antagonist activity.

18. A process for producing an acylaminopyridine compound (A3) represented by the following formula:



(A3)

(wherein L^1, R^2, R^3, Ar, Q and W have the same meanings as defined below, respectively), a salt thereof or hydrates thereof, which comprises allowing an aminopyridine compound (A2) represented by the following formula:



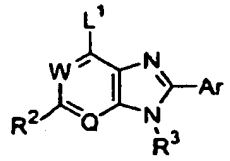
(A2)

(wherein L^1 represents a halogen atom; R^2 represents 1) hydrogen, 2) a halogen atom, , 3) a C2-C8 alkynyl group a4) a C1-C8 alkyl group, or 5) a C1-C8 alkoxy group; R^3 represents a 1,2-dihydro-2-oxopyridyl group which may be substituted with a) a halogen atom or a C1-C6 alkyl group, and whose nitrogen atom may further be substituted with b-1) a C1-C6 alkyl group which may be substituted with a halogen atom, hydroxyl or an optionally protected carboxyl group, b-2) an optionally substituted C3-C6 cycloalkyl-C1-C4 alkyl group or b-3) an optionally substituted C3-C6 cycloalkyl group, and Q and W are both N or one of Q and W is N and the other is CH), to react with an acyl compound represented by the formula ArCOX (wherein X represents a halogen atom; and Ar represents 1) an optionally substituted phenyl group, 2) an optionally substituted pyridyl group, 3) an optionally substituted furyl group, or 4) an optionally substituted thienyl group.

19. A process for producing an acylaminopyridine compound (A3) according to claim 18, wherein the aminopyridine compound (A2) is reacted in the presence of pyridine with the acyl compound represented by the formula ArCOX.

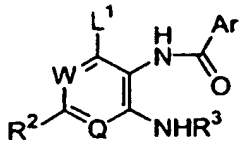
20. The process for producing an acylaminopyridine compound (A3), a salt thereof or hydrates thereof according to claim 18 or 19, wherein R^3 is an N-Cl-C8 alkyl-2-oxopyrimidinyl group.

21. A process for producing an imidazopyridine compound (A4), a salt thereof or hydrates thereof represented by the following formula:



(A4)

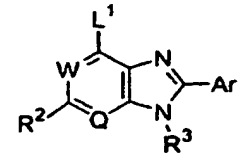
(wherein L^1, R^2, R^3, Ar, Q and W have the same meanings as defined in claim 18, respectively), which comprises subjecting an acylaminopyridine compound (A3) represented by the following formula:



(A3)

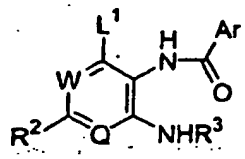
(wherein L^1, R^2, R^3, Ar, Q and W have the same meanings as defined in claim 18, respectively) to ring-closure reaction in the presence of $POCl_3$.

22. A process for producing an imidazopyridine compound (A4), a salt thereof or hydrates thereof represented by the following formula:



(A4)

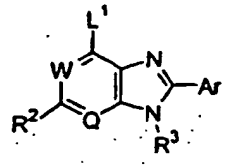
(wherein L^1, R^2, R^3, Ar, Q and W have the same meanings as defined in claim 18, respectively), which comprises subjecting an acylaminopyridine compound (A3) represented by the following formula:



(A3)

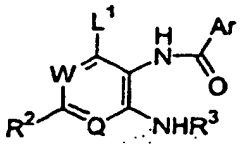
(wherein L^1, R^2, R^3, Ar, Q and W have the same meanings as defined in claim 18, respectively) to ring-closure reaction in the presence of hydrochloric acid or using hydrochloride of an acylaminopyridine compound (A3).

23. A process for producing an imidazopyridine compound (A4), a salt thereof or hydrates thereof represented by the following formula:



(A4)

(wherein L^1, R^2, R^3, Ar, Q and W have the same meanings as defined in claim 18, respectively), which comprises subjecting an acylaminopyridine compound (A3) represented by the following formula:

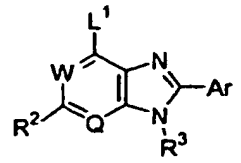


(A3)

(wherein L^1, R^2, R^3, Ar, Q and W have the same meanings as defined in claim 18, respectively) to ring-closure reaction in NMP (1-methyl-2-pyrrolidone) under heating.

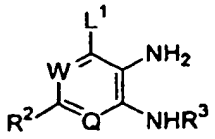
24. The process for producing an imidazopyridine compound (A4), a salt thereof or hydrates thereof according to claims 19 to 23, wherein R^3 is an N-C1-C8 alkyl-2-oxopyridinyl group.

25. A process for producing an imidazopyridine compound (A4), a salt thereof or hydrates thereof represented by the following formula:



(A4)

(wherein L^1, R^2, R^3, Ar, Q and W have the same meanings as defined in claim 18, respectively), which comprises allowing an aminopyridine compound (A2) represented by the following formula:

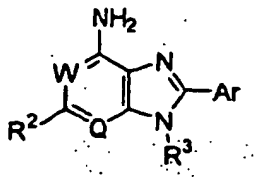


(A2)

(wherein L^1, R^2, R^3, Q and W have the same meanings as defined in claim 18, respectively) to react with an acyl compound represented by the formula ArCOX (wherein X and Ar have the same meanings as defined in claim 18, respectively); and then subjecting the product to ring-closure reaction.

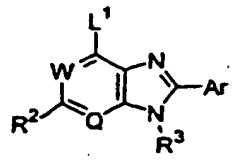
26. The process for producing an imidazopyridine compound (A4), a salt thereof or hydrates thereof according to claim 25, wherein the aminopyridine compound (A2) is converted in one-pot reaction into the imidazopyridine compound (A4).

27. A process for producing an aminoimidazopyridine compound (A5), a salt thereof or hydrates thereof represented by the formula:



(A5)

(wherein L^1, R^2, R^3, Ar, Q and W have the same meanings as defined in claim 18, respectively), which comprises aminating an imidazopyridine compound (A4) represented by the following formula:

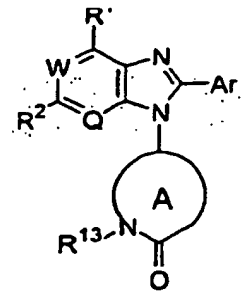


(A4)

(wherein L^1, R^2, R^3, Ar, Q and W have the same meanings as defined in claim 18, respectively).

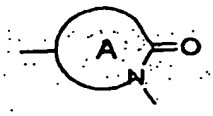
28. The process for producing an aminoimidazopyridine compound (A5), a salt thereof or hydrates thereof according to claim 27, wherein R^3 is an N-C1-C8 alkyl-2-oxopyridinyl group.

29. A process for producing an imidazopyridine compound (C3), a salt thereof or hydrates thereof represented by the formula:

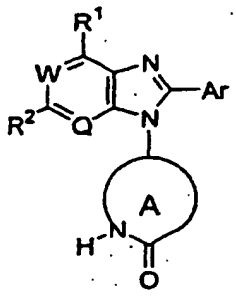


(C3)

(wherein R^{13} means a C1-C6 alkyl group which may be substituted with a halogen atom, hydroxyl or an optionally protected carboxyl group, an optionally substituted C3-C6 cycloalkyl-C1-C4 alkyl group, or an optionally substituted C3-C6 cycloalkyl group; the formula:

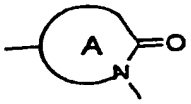


represents dihydro oxopyridinyl; and R^1 R^2, Ar, Q and W have the same meanings as defined in claim 18, respectively), which comprises alkylating an imidazopyridine compound (C2) represented by the following formula:



(C2)

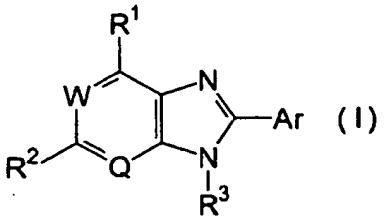
(wherein R^1 represents hydrogen atom or formula $-NR^4R^5$ (wherein R^4 and R^5 are the same as or different from each other and each represents hydrogen atom or a C1-C8 alkyl group); the formula:



represents dihydrooxopyridinyl; and R^2, Ar, Q and W have the same meanings as defined above, respectively).

Patentansprüche

1. Kondensierte Imidazolverbindung, deren pharmakologisch annehmbares Salz oder Hydrat, dargestellt durch die Formel (I):



(I)

worin R^1 Wasserstoff oder die Formel $-NR^4R^5$ darstellt (worin R^4 und R^5 gleich oder voneinander verschieden sind und jeweils Wasserstoff, eine C_{3-8}-Cycloalkylgruppe oder eine C_{1-8}-Alkylgruppe darstellen); R^2 (1) Wasserstoff, (2) ein Halogenatom, (3) eine C_{2-8}-Alkinylgruppe, die mit einer Hydroxylgruppe oder einer C_{3-6}-Cycloalkylgruppe substituiert sein kann, (4) eine C_{1-8}-Alkylgruppe oder (5) eine C_{1-8}-Alkoxygruppe darstellt; R^3 eine 1,2-Dihydro-2-oxopyridyl-Gruppe darstellt, die mit (a) einem Halogenatom oder einer C_{1-6}-Alkylgruppe substituiert sein kann, und deren Stickstoffatom ferner mit (b-1) einer C_{1-6}-Alkylgruppe, die mit einem Halogenatom, Hydroxyl, Phenyl, C_{2-8}-Alkenyl oder einer optional geschützten Carboxylgruppe substituiert sein kann, (b-2) einer optional substituierten C_{3-6}-Cycloalkyl-C_{1-4}-alkyl-Gruppe oder (b-3) einer optional substituierten C_{3-6}-Cycloalkylgruppe substituiert

sein kann; Ar (1) eine optional substituierte Phenylgruppe, (2) eine optional substituierte Pyridylgruppe, (3) eine optional substituierte Furylgruppe oder (4) eine optional substituierte Thienylgruppe darstellt; und Q und W beide N sind oder eines von Q und W N und das andere CH ist.

2. Kondensierte Imidazolverbindung gemäss Anspruch 1, deren pharmakologisch annehmbares Salz oder Hydrat, worin R^2 ein Wasserstoffatom ist.

3. Kondensierte Imidazolverbindung gemäss Anspruch 1 oder 2, deren pharmakologisch annehmbares Salz oder Hydrat, worin Ar ein optional substituiertes Phenyl ist.

4. Kondensierte Imidazolverbindung gemäss einem der Ansprüche 1 bis 3, deren pharmakologisch annehmbares Salz oder Hydrat, worin Ar ein mit einem Halogenatom substituiertes Phenyl ist.

5. Kondensierte Imidazolverbindung gemäss einem der Ansprüche 1 bis 4, deren pharmakologisch annehmbares Salz oder Hydrat, worin R^1 durch die Formel NR^4R^5 dargestellt wird (worin R^4 und R^5 gleich oder voneinander verschieden sind und jeweils Wasserstoff oder eine C_{1-8}-Alkylgruppe darstellen).

6. Kondensierte Imidazolverbindung gemäss einem der Ansprüche 1 bis 5, deren pharmakologisch annehmbares Salz oder Hydrat, worin R^1 Amino ist.

7. Kondensierte Imidazolverbindung gemäss einem der Ansprüche 1 bis 6, deren pharmakologisch annehmbares Salz oder Hydrat, worin R^1 Amino und R^2 Wasserstoff ist.

8. Kondensierte Imidazolverbindung gemäss einem der Ansprüche 1 bis 7, deren pharmakologisch annehmbares Salz oder Hydrat, worin R^1 Amino, R^2 Wasserstoff und R^3 eine 1,2-Dihydro-2-oxopyridyl-Gruppe ist, deren Stickstoff mit einer C_{1-6}-Alkylgruppe substituiert sein kann, die mit einem Halogenatom substituiert sein kann.

9. Kondensierte Imidazolverbindung gemäss Anspruch 1, die 5-[6-Amino-8-(3-fluorphenyl)-9H-9-purinyl]-1-methyl-1,2-dihydro-2-pyridinon und deren pharmakologisch annehmbares Salz oder Hydrat ist.

10. Kondensierte Imidazolverbindung gemäss Anspruch 1, deren pharmakologisch annehmbares Salz oder Hydrat, die eine Purinverbindung ist, worin jedes von Q und W Stickstoff bedeutet.

11. Kondensierte Imidazolverbindung gemäss Anspruch 1, deren pharmakologisch annehmbares Salz oder Hydrat, die eine Imidazopyridinverbindung ist, worin eines von Q und W N und das andere -CH ist.

12. Kondensierte Imidazolverbindung gemäss Anspruch 1, deren pharmakologisch annehmbares Salz oder Hydrat, die 5-{6-Amino-8-(3-fluorphenyl)-2-[2-(1-hydroxycyclobutyl)-1-ethinyl]-9H-9-purinyl}-1-methyl-1,2-dihydro-2-pyridon ist.

13. Pharmazeutische Zusammensetzung, umfassend die kondensierte Imidazolverbindung gemäss einem der Ansprüche 1 bis 12, deren pharmakologisch annehmbares Salz oder Hydrat und optional einen pharmakologisch annehmbaren Träger.

14. Verwendung der kondensierten Imidazolverbindung gemäss einem der Ansprüche 1 bis 12, deren pharmakologisch annehmbares Salz oder Hydrat zur Herstellung eines Medikaments zur Verhinderung oder Behandlung von Diabetes mellitus.

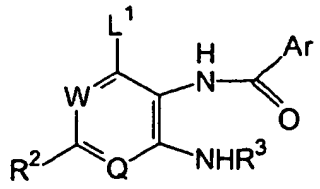
15. Verwendung der kondensierten Imidazolverbindung gemäss einem der Ansprüche 1 bis 12, deren pharmakologisch annehmbares Salz oder Hydrat zur Herstellung eines Medikaments zur Verhinderung oder Behandlung von diabetischen Komplikationen.

16. Verwendung der kondensierten Imidazolverbindung gemäss einem der Ansprüche 1 bis 12, deren pharmakologisch annehmbares Salz oder Hydrat zur Herstellung eines Medikaments zur Verhinderung oder Behandlung von diabetischer Retinopathie.

17. Verwendung der kondensierten Imidazolverbindung gemäss einem der Ansprüche 1 bis 12, deren pharmakologisch annehmbares Salz oder Hydrat zur Herstellung eines Medikaments mit antagonistischer Aktivität gegenüber

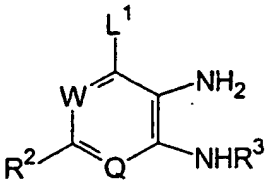
dem Adenosin A2-Rezeptor.

18. Verfahren zur Herstellung einer durch die folgende Formel dargestellten Acylaminopyridinverbindung (A3):



(A3)

(worin L^1, R^2, R^3, Ar, Q bzw. W dieselben Bedeutungen wie unten definiert haben), deren Salz oder Hydrat, das das Umsetzen einer durch die folgende Formel dargestellten Aminopyridinverbindung (A2):



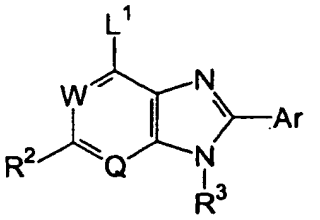
(A2)

(worin L^1 ein Halogenatom darstellt; R^2 (1) Wasserstoff, (2) ein Halogenatom, (3) eine C_{2-8}-Alkinylgruppe, (4) eine C_{1-8}-Alkylgruppe oder (5) eine C_{1-8}-Alkoxygruppe darstellt; R^3 eine 1,2-Dihydro-2-oxopyridyl-Gruppe darstellt, die mit (a) einem Halogenatom oder einer C_{1-6}-Alkylgruppe substituiert sein kann, und deren Stickstoffatom ferner mit (b-1) einer C_{1-6}-Alkylgruppe, die mit einem Halogenatom, Hydroxyl oder einer optional geschützten Carboxylgruppe substituiert sein kann, (b-2) einer optional substituierten C_{3-6}-Cycloalkyl-C_{1-4}-alkyl-Gruppe oder (b-3) einer optional substituierten C_{3-6}-Cycloalkylgruppe substituiert sein kann; und Q und W beide N sind oder eines von Q und W N und das andere CH ist), mit einer durch die Formel ArCOX dargestellten Acylverbindung (worin X ein Halogenatom darstellt; und Ar (1) eine optional substituierte Phenylgruppe, (2) eine optional substituierte Pyridylgruppe, (3) eine optional substituierte Furylgruppe oder (4) eine optional substituierte Thienylgruppe darstellt) umfasst.

19. Verfahren zur Herstellung einer Acylaminopyridinverbindung (A3) gemäss Anspruch 18, worin die Aminopyridinverbindung (A2) in Gegenwart von Pyridin mit der durch die Formel ArCOX dargestellten Acylverbindung umgesetzt wird.

20. Verfahren zur Herstellung einer Acylaminopyridinverbindung (A3), deren Salz oder Hydrat gemäss Anspruch 18 oder 19, worin R^3 eine N-C_{1-8}-Alkyl-2-oxopyrimidinyl-Gruppe ist.

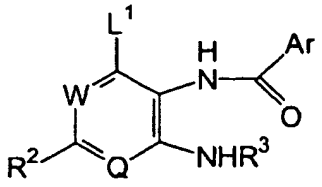
21. Verfahren zur Herstellung einer durch die folgende Formel dargestellten Imidazopyridinverbindung (A4), deren Salz oder Hydrat:



(A4)

(worin L^1, R^2, R^3, Ar, Q bzw. W dieselben Bedeutungen wie in Anspruch 18 definiert haben), das das Unterwerfen

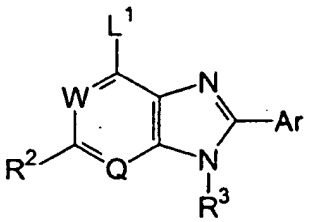
einer durch die folgende Formel dargestellten Acylaminopyridinverbindung (A3):



(A3)

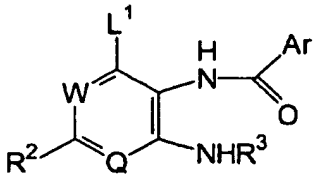
(worin L^1, R^2, R^3, Ar, Q bzw. W dieselben Bedeutungen wie in Anspruch 18 definiert haben) einer Ringschlussreaktion in Gegenwart von $POCl_3$ umfasst.

22. Verfahren zur Herstellung einer durch die folgende Formel dargestellten Imidazopyridinverbindung (A4), deren Salz oder Hydrat:



(A4)

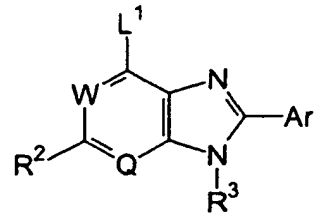
(worin L^1, R^2, R^3, Ar, Q bzw. W dieselben Bedeutungen wie in Anspruch 18 definiert haben), das das Unterwerfen einer durch die folgende Formel dargestellten Acylaminopyridinverbindung (A3):



(A3)

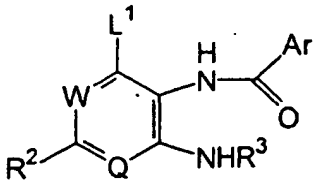
(worin L^1, R^2, R^3, Ar, Q bzw. W dieselben Bedeutungen wie in Anspruch 18 definiert haben) einer Ringschlussreaktion in Gegenwart von Salzsäure oder unter Verwendung eines Hydrochlorids der Acylaminopyridinverbindung (A3) umfasst.

23. Verfahren zur Herstellung einer durch die folgende Formel dargestellten Imidazopyridinverbindung (A4), deren Salz oder Hydrat:



(A4)

(worin L^1, R^2, R^3, Ar, Q bzw. W dieselben Bedeutungen wie in Anspruch 18 definiert haben), das das Unterwerfen einer durch die folgende Formel dargestellten Acylaminopyridinverbindung (A3):

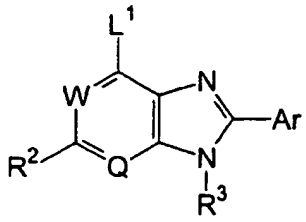


(A3)

(worin L^1, R^2, R^3, Ar, Q bzw. W dieselben Bedeutungen wie in Anspruch 18 definiert haben) einer Ringschlussreaktion in NMP (1-Methyl-2-pyrrolidon) unter Erwärmen umfasst.

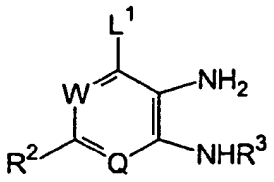
24. Verfahren zur Herstellung einer Imidazopyridinverbindung (A4), deren Salz oder Hydrat gemäss Ansprüchen 19 bis 23, worin R^3 eine N-C_{1-8}-Alkyl-2-oxopyridinyl-Gruppe ist.

25. Verfahren zur Herstellung einer durch die folgende Formel dargestellten Imidazopyridinverbindung (A4), deren Salz oder Hydrat:



(A4)

(worin L^1, R^2, R^3, Ar, Q bzw. W dieselben Bedeutungen wie in Anspruch 18 definiert haben), das das Umsetzen einer durch die folgende Formel dargestellten Aminopyridinverbindung (A2):

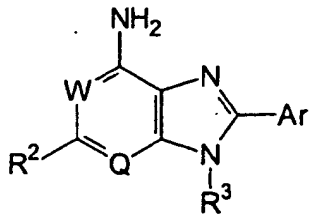


(A2)

(worin L^1, R^2, R^3, Q bzw. W dieselben Bedeutungen wie in Anspruch 18 definiert haben) mit einer durch die Formel ArCOX dargestellten Acylverbindung (worin X und Ar dieselben Bedeutungen wie in Anspruch 18 definiert haben); und dann Unterwerfen des Produkts einer Ringschlussreaktion umfasst.

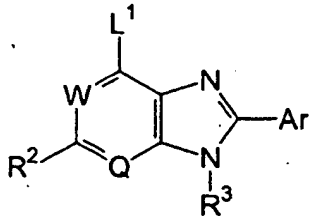
26. Verfahren zur Herstellung einer Imidazopyridinverbindung (A4), deren Salz oder Hydrat gemäss Anspruch 25, worin die Aminopyridinverbindung (A2) in einer Ein-Topf-Reaktion in die Imidazopyridinverbindung (A4) überführt wird.

27. Verfahren zur Herstellung einer durch die folgende Formel dargestellten Aminoimidazopyridinverbindung (A5), deren Salz oder Hydrat:



(A5)

(worin L^1, R^2, R^3, Ar, Q bzw. W dieselben Bedeutungen wie in Anspruch 18 definiert haben), das das Aminieren einer durch die folgende Formel dargestellten Imidazopyridinverbindung (A4):

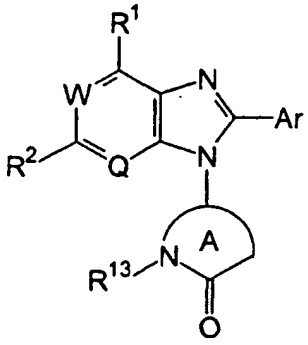


(A4)

(worin L^1, R^2, R^3, Ar, Q bzw. W dieselben Bedeutungen wie in Anspruch 18 definiert haben) umfasst.

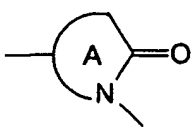
28. Verfahren zur Herstellung einer Aminoimidazopyridinverbindung (A5), deren Salz oder Hydrat gemäss Anspruch 27, worin R^3 eine N-C_{1-6}-Alkyl-2-oxopyridinyl-Gruppe ist.

29. Verfahren zur Herstellung einer durch die folgende Formel dargestellten Imidazopyridinverbindung (C3), deren Salz oder Hydrat:



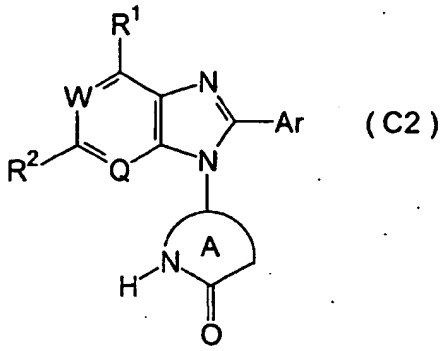
(C3)

(worin R^{13} eine C_{1-6}-Alkylgruppe bedeutet, die mit einem Halogenatom, Hydroxyl oder einer optional geschützten Carboxylgruppe, einer optional substituierten C_{3-6}-Cycloalkyl-C_{1-4}-alkyl-Gruppe oder einer optional substituierten C_{3-6}-Cycloalkylgruppe substituiert sein kann; die Formel:



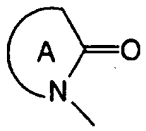
Dihydrooxopyridinyl darstellt; und R^1, R^2, Ar, Q bzw. W dieselben Bedeutungen wie in Anspruch 18 definiert haben),

das das Alkylieren einer durch die folgende Formel dargestellten Imidazopyridinverbindung (C2):



(C2)

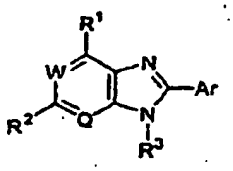
(worin R^1 ein Wasserstoffatom oder die Formel $-NR^4R^5$ darstellt (worin R^4 und R^5 gleich oder voneinander verschieden sind und jeweils ein Wasserstoffatom oder eine C_{1-8}-Alkylgruppe darstellen); die Formel:



Dihydrooxopyridinyl darstellt; und R^2, Ar, Q bzw. W dieselben Bedeutungen wie oben definiert haben) umfasst.

Revendications

1. Composé d'imidazole condensé, sel pharmacologiquement acceptable de celui-ci ou hydrates de celui-ci, qui est représenté par la formule (I) :



(I)

(dans laquelle R^1 représente un hydrogène ou la formule $-NR^4R^5$ (dans laquelle R^4 et R^5 sont identiques ou différents l'un de l'autre et chacun représente un hydrogène, un groupe cycloalkyle en C_3-C_8 ou un groupe alkyle en C_1-C_8) ; R^2 représente 1) un hydrogène, 2) un atome d'halogène, 3) un groupe alcynyle en C_2-C_8, qui peut être substitué par un groupe hydroxyle ou un groupe cycloalkyle en C_3-C_6, 4) un groupe alkyle en C_1-C_8, ou 5) un groupe alcoxy en C_1-C_8 ; R^3 représente un groupe 1,2-dihydro-2-oxopyridyle qui peut être substitué par a) un atome d'halogène ou un groupe alkyle en C_1-C_6, et dont l'atome d'azote peut en outre être substitué par b-1) un groupe alkyle en C_1-C_6 qui peut être substitué par un atome d'halogène, un groupe hydroxyle, un groupe phényle, un groupe alcényle en C_2-C_8 ou un groupe carboxyle éventuellement protégé, b-2) un groupe (cycloalkyl en C_3-C_6) alkyle en C_1-C_4 éventuellement substitué, ou b-3) un groupe cycloalkyle en C_3-C_6 éventuellement substitué ; Ar représente 1) un groupe phényle éventuellement substitué, 2) un groupe pyridyle éventuellement substitué, 3) un groupe furyle éventuellement substitué, ou 4) un groupe thiényle éventuellement substitué ; et Q et W sont tous deux N ou l'un de Q et W est N et l'autre est CH).

2. Composé d'imidazole condensé selon la revendication 1, sel pharmacologiquement acceptable de celui-ci ou hydrates de celui-ci, dans lequel R^2 est un atome d'hydrogène.

3. Composé d'imidazole condensé selon la revendication 1 ou 2, sel pharmacologiquement acceptable de celui-ci ou hydrates de celui-ci, dans lequel Ar est un groupe phényle éventuellement substitué.

4. Composé d'imidazole condensé selon l'une quelconque des revendications 1 à 3, sel pharmacologiquement acceptable de celui-ci ou hydrates de celui-ci, dans lequel Ar est un groupe phényle substitué par un atome d'halogène.

5. Composé d'imidazole condensé selon l'une quelconque des revendications 1 à 4, sel pharmacologiquement acceptable de celui-ci ou hydrates de celui-ci, dans lequel R^1 est représenté par la formule $-NR^4R^5$ (dans laquelle R^4 et R^5 sont identiques ou différents l'un de l'autre et chacun représente un hydrogène ou un groupe alkyle en C_1-C_8).

6. Composé d'imidazole condensé selon l'une quelconque des revendications 1 à 5, sel pharmacologiquement acceptable de celui-ci ou hydrates de celui-ci, dans lequel R^1 est un groupe amino.

7. Composé d'imidazole condensé selon l'une quelconque des revendications 1 à 6, sel pharmacologiquement acceptable de celui-ci ou hydrates de celui-ci, dans lequel R^1 est un groupe amino et R^2 est un hydrogène.

8. Composé d'imidazole condensé selon l'une quelconque des revendications 1 à 7, sel pharmacologiquement acceptable de celui-ci ou hydrates de celui-ci, dans lequel R^1 est un groupe amino, R^2 est un hydrogène, et R^3 est un groupe 1,2-dihydro-2-oxopyridyle dont l'azote peut être substitué par un groupe alkyle en C_1 à C_6 qui peut être substitué par un atome d'halogène.

9. Composé d'imidazole condensé selon la revendication 1, qui est la 5-[6-amino-8-(3-fluorophényl)-9H-9-purinyl]-1-méthyl-1,2-dihydro-2-pyridinone, et un sel pharmacologiquement acceptable de celui-ci ou des hydrates de celui-ci.

10. Composé d'imidazole condensé selon la revendication 1, sel pharmacologiquement acceptable de celui-ci ou hydrates de celui-ci, qui est un composé de purine dans lequel chacun de Q et W représente un azote.

11. Composé d'imidazole condensé selon la revendication 1, sel pharmacologiquement acceptable de celui-ci ou hydrates de celui-ci, qui est un composé d'imidazopyridine dans lequel l'un de Q et W est N et l'autre est CH.

12. Composé d'imidazole condensé selon la revendication 1, sel pharmacologiquement acceptable de celui-ci ou hydrates de celui-ci, qui est la 5-{6-amino-8-(3-fluorophényl)-2-[2-(1-hydroxycyclobutyl)-1-éthynyl]-9H-9-purinyl}-1-méthyl-1,2-dihydro-2-pyridinone.

13. Composition pharmaceutique comprenant le composé d'imidazole condensé selon l'une quelconque des revendications 1 à 12, un sel pharmacologiquement acceptable de celui-ci ou des hydrates de celui-ci, et éventuellement un support pharmacologiquement acceptable.

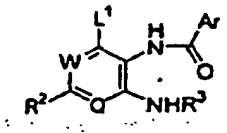
14. Utilisation du composé d'imidazole condensé selon l'une quelconque des revendications 1 à 12, d'un sel pharmacologiquement acceptable de celui-ci ou des hydrates de celui-ci, pour la préparation d'un médicament destiné à prévenir ou traiter un diabète mellitus.

15. Utilisation du composé d'imidazole condensé selon l'une quelconque des revendications 1 à 12, d'un sel pharmacologiquement acceptable de celui-ci ou des hydrates de celui-ci, pour la préparation d'un médicament destiné à prévenir ou traiter des complications diabétiques.

16. Utilisation du composé d'imidazole condensé selon l'une quelconque des revendications 1 à 12, d'un sel pharmacologiquement acceptable de celui-ci ou des hydrates de celui-ci, pour la préparation d'un médicament destiné à prévenir ou traiter une rétinopathie diabétique.

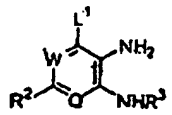
17. Utilisation du composé d'imidazole condensé selon l'une quelconque des revendications 1 à 12, d'un sel pharmacologiquement acceptable de celui-ci ou des hydrates de celui-ci, pour la préparation d'un médicament possédant une activité antagoniste des récepteurs A2 de l'adénosine.

18. Procédé de production d'un composé d'acylaminopyridine (A3) représenté par la formule suivante :



(A3)

(dans laquelle L^1, R^2, R^3, Ar, Q et W possèdent les mêmes significations que ci-dessous, respectivement), d'un sel de celui-ci ou des hydrates de celui-ci, qui conmprend de faire réagir un dérivé d'aminopyridine (A2) représenté par la formule suivante :



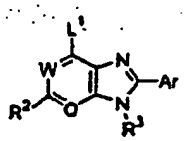
(A2)

(dans laquelle L^1 représente un atome d'halogène ; R^2 représente 1) un hydrogène, 2) un atome d'halogène, 3) un groupe alcynyle en C_2-C_8, 4) un groupe alkyle en C_1-C_8, ou 5) un groupe alcoxy en C_1-C_8 ; R^3 représente un groupe 1,2-dihydro-2-oxopyridyle qui peut être substitué par a) un atome d'halogène ou un groupe alkyle en C_1-C_6, et dont l'atome d'azote peut en outre être substitué par b-1) un groupe alkyle en C_1-C_6 qui peut être substitué par un atome d'halogène, un groupe hydroxyle ou un groupe carboxyle éventuellement protégé, b-2) un groupe (cycloalkyl en C_3-C_6)alkyle en C_1-C_4 éventuellement substitué, ou b-3) un groupe cycloalkyle en C_3-C_6 éventuellement substitué ; et Q et W sont tous deux N ou l'un de Q et W est N et l'autre est CH), avec un composé d'acyle représenté par la formule ArCOX (dans laquelle X représente un atome d'halogène ; et Ar représente 1) un groupe phényle éventuellement substitué, 2) un groupe pyridyle éventuellement substitué, 3) un groupe furyle éventuellement substitué, ou 4) un groupe thiényle éventuellement substitué).

19. Procédé de production d'un composé d'acylaminopyridine (A3) selon la revendication 18, dans lequel on fait réagir le composé d'aminopyridine (A2) en présence de pyridine avec le composé d'acyle représenté par la formule ArCOX.

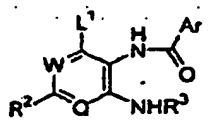
20. Procédé de production d'un composé d'acylaminopyridine (A3), d'un sel de celui-ci ou des hydrates de celui-ci selon la revendication 18 ou 19, dans lequel R^3 est un groupe N-(alkyl en C_1-C_8)-2-oxopyrimidinyle.

21. Procédé de production d'un composé d'imidazopyridine (A4), d'un sel de celui-ci ou des hydrates de celui-ci, représenté par la formule suivante :



(A4)

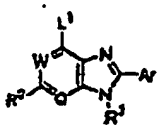
(dans laquelle L^1, R^2, R^3, Ar, Q et W possèdent les mêmes significations que celles définies dans la revendication 18, respectivement), qui comprend de soumettre un composé d'acylaminopyridine (A3) représenté par la formule suivante :



(A3)

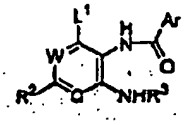
(dans laquelle L^1, R^2, R^3, Ar, Q et W possèdent les mêmes significations que celles définies dans la revendication 18, respectivement) à une réaction de fermeture de cycle en présence de $POCl_3$.

22. Procédé de production d'un composé d'imidazopyridine (A4), d'un sel de celui-ci ou des hydrates de celui-ci, représenté par la formule suivante :



(A4)

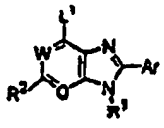
(dans laquelle L^1, R^2, R^3, Ar, Q et W possèdent les mêmes significations que celles définies dans la revendication 18, respectivement), qui comprend de soumettre un composé d'acylaminopyridine (A3) représenté par la formule suivante :



(A3)

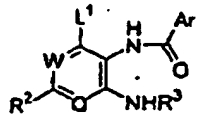
(dans laquelle L^1, R^2, R^3, Ar, Q et W possèdent les mêmes significations que celles définies dans la revendication 18, respectivement) à une réaction de fermeture de cycle en présence d'acide chlorhydrique ou en utilisant le chlorhydrate d'un composé d'acylaminopyridine (A3).

23. Procédé de production d'un composé d'imidazopyridine (A4) d'un sel de celui-ci ou des hydrates de celui-ci, représenté par la formule suivante :



(A4)

(dans laquelle L^1, R^2, R^3, Ar, Q et W possèdent les mêmes significations que celles définies dans la revendication 18, respectivement), qui comprend de soumettre un composé d'acylàminopyridine (A3) représenté par la formule suivante :

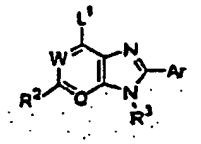


(A3)

(dans laquelle L^1, R^2, R^3, Ar, Q et W possèdent les mêmes significations que celles définies dans la revendication 18, respectivement) à une réaction de fermeture de cycle dans de la NMP (1-méthyl-2-pyrrolidone) sous chauffage.

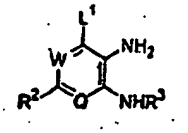
24. Procédé de production d'un composé d'imidazopyridine (A4), d'un sel de celui-ci ou des hydrates de celui-ci selon les revendications 19 à 23, dans lequel R^3 est un groupe N-(alkyl en C_1-C_8)-2-oxopyridinyle.

25. Procédé de production d'un composé d'imidazopyridine (A4), d'un sel de celui-ci ou des hydrates de celui-ci, représenté par la formule suivante :



(A4)

(dans laquelle L^1, R^2, R^3, Ar, Q et W possèdent les mêmes significations que celles définies dans la revendication 18, respectivement), qui comprend de faire réagir un composé d'aminopyridine (A2) représenté par la formule suivante :

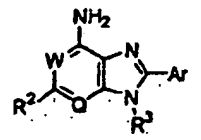


(A2)

(dans laquelle L^1, R^2, R^3, Q et W possèdent les mêmes significations que celles définies dans la revendication 18, respectivement) avec un composé d'acyle représenté par la formule ArCOX (dans laquelle X et Ar possèdent les mêmes significations que celles définies dans la revendication 18, respectivement) ; puis de soumettre le produit à une réaction de fermeture de cycle.

26. Procédé de production d'un composé d'imidazopyridine (A4), d'un sel de celui-ci ou des hydrates de celui-ci selon la revendication 25, dans lequel le composé d'aminopyridine (A2) est transformé dans une réaction en un seul pot en composé d'imidazopyridine (A4).

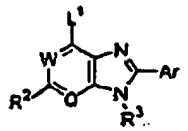
27. Procédé de production d'un composé d'aminoimidazopyridine (A5), d'un sel de celui-ci ou des hydrates de celui-ci, représenté par la formule suivante :



(A5)

(dans laquelle L^1, R^2, R^3, Q et W possèdent les mêmes significations que celles définies dans la revendication

18, respectivement), qui comprend d'aminer un composé d'imidazopyridine (A4) représenté par la formule suivante :

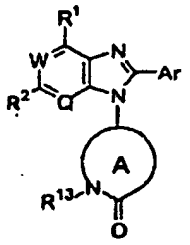


(A4)

(dans laquelle L^1, R^2, R^3, Ar, Q et W possèdent les mêmes significations que celles définies dans la revendication 18, respectivement).

28. Procédé de production d'un composé d'aminoimidazopyridine (A5), d'un sel de celui-ci ou des hydrates de celui-ci selon la revendication 27, dans lequel R^3 est un groupe N-(alkyl en C_1-C_8)-2-oxopyridinyle.

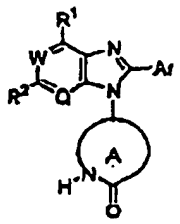
29. Procédé de production d'un composé d'imidazopyridine (C3), d'un sel de celui-ci ou d'un hydrate de celui-ci, représenté par la formule suivante :



(C3)

(dans laquelle R^{13} représente un groupe alkyle en C_1-C_6 qui peut être substitué par un atome d'halogène, un groupe hydroxyle ou un groupe carboxyle éventuellement protégé, un groupe (cycloalkyl en C_3-C_6)-alkyle en C_1-C_4 éventuellement substitué, ou un groupe cycloalkyle en C_3-C_6 éventuellement substitué ; la formule :

représente un groupe dihydrooxopyridinyle ; et R^1, R^2, Ar, Q et W possèdent les mêmes significations que celles définies dans la revendication 18, respectivement), qui comprend d'alkyler un composé d'imidazopyridine (C2) représenté par la formule suivante :



(C2)

(dans laquelle R^1 représente un atome d'hydrogène ou la formule $-NR^4R^5$ (dans laquelle R^4 et R^5 sont identiques ou différents l'un de l'autre et chacun représente un hydrogène ou un groupe alkyle en C_1-C_8) ; la formule :

représente un groupe dihydrooxopyridinyle ; et R^2, Ar, Q et W possèdent les mêmes significations que celles définies ci-dessus, respectivement).